UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

#24

NOV 20 2001

David T. Read
Acting Director Health Assessment Policy Staff, CDER
Food and Drug Administration
1451 Rockville Pike, HFD-7
Rockville, MD 20852

Dear Mr. Read:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 4,690,951. The application was filed on February 18, 2000, under 35 U.S.C. § 156.

The patent claims a product that was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term restoration. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (703) 306-3159 (telephone) or (703)872-9411 (facsimile).

Karin Tyson
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Frederick D. Hunter
Eli Lilly & Co.
Patent Division (FDH), Lilly Corporate Center
Indianapolis IN 46285

Re: Paylean
Docket No. 01E-0229

Ractopamine Patent Extension
Exhibit Listing

Exhibit No.:	Description:
I	Label for Paylean™
II	Copy of U.S. Patent 4,690,951
III	Certificate of Correction
IV	Maintenance Fee Receipt
V	Letter Transmitting INAD to FDA
VI	Copy of FDA Letter Acknowledging Receipt and Assigning INAD No. 4231
VII	Letter Transmitting NADA to fDA
VIII	FDA Letter Acknowledging Receipt
IX	FDA Approval Letter
X	Description of Significant Activities
XI	U.S. Patent 4,734,437
XII	U.S. Patent 4,849,453
XIII	U.S. Patent 4,992,473
XIV	U.S. Patent 5,643,967

Exhibit I

Label for Paylean™

ELANCO

AF0602-25B

For Use in Finishing Swine Feeds Only

Paylean® 9

Ractopamine Hydrochloride

Net Weight 25 lb
(11.34 kg)

Type A Medicated Article

Do not feed undiluted.

Active Drug Ingredient: ractopamine hydrochloride – 9 g per lb (20 g per kg)

Important: Must be thoroughly mixed into feeds before use. Follow label directions.

Indication: For increased rate of weight gain, improved feed efficiency, and increased carcass leanness in finishing swine fed a complete ration containing at least 16% crude protein from 150 lb (68 kg) to 240 lb (109 kg) body weight.

Indications	Appropriate Concentration of Ractopamine in Type C Medicated Feed
Increased Rate of Weight Gain, Improved Feed Efficiency, and Increased Carcass Leanness	4.5 grams/ton (5 ppm)
Improved Feed Efficiency and Increased Carcass Leanness	4.5 to 18 grams/ton (5 ppm to 20 ppm)

Inert Ingredients: Ground corncobs.

Carcass Measurements	Effect of Ractopamine	
	4.5 grams/ton (5 ppm)	9 - 18 grams/ton (10 - 20 ppm)
Carcass Fat	NC	↓
10th Rib Backfat (3/4 location)	NC	↓
Last Rib Backfat (midline)	NC	NC
Loineye Area (10th rib)	NC	↑
Rate of Lean Gain	NC	↑
Efficiency of Lean Gain	NC	↑
Dressing Percentage	NC	↑

NC= No Change, ↑ = increased, ↓ = decreased

Mixing Directions: Thoroughly mix Paylean 9 Type A Medicated Article into one ton of appropriate feed ingredients or diluents according to the table below to obtain the proper concentration in the Type B Medicated Feed (maximum 3600 g/ton). The following table gives examples of how some Type B Medicated Feed concentrations can be prepared:

Pounds of Paylean 9 To Add Per Ton To Make a Type B Medicated Feed	Resulting Ractopamine Concentration in Type B Medicated Feed	
	grams/ton	grams/pound
100	900	0.45
200	1,800	0.90
300	2,700	1.35
400	3,600	1.80

Thoroughly mix Paylean 9 Type A Medicated Article into one ton of complete swine feed according to the table below to obtain the proper concentration in the Type C Medicated Feed. Prepare an intermediate pre-blend of the premix prior to mixing in a complete feed. Thoroughly mix the required amount in a convenient quantity of feed ingredients then add to the remaining feed ingredients to make a ton of complete feed.

Pounds Paylean 9 To Add Per Ton of Type C Medicated Feed	Resulting Ractopamine Concentration in Type C Medicated Feed
0.5	4.5 grams/ton (5 ppm)
1.0	9 grams/ton (10 ppm)
1.5	13.5 grams/ton (15 ppm)
2.0	18 grams/ton (20 ppm)

Feeding Directions: Feed continuously to finishing swine as the sole ration from 150 lb (68 kg) to 240 lb (109 kg) body weight.

CAUTION: Not for use in breeding swine.

WARNING: The active ingredient in Paylean, ractopamine hydrochloride, is a beta-adrenergic agonist. Individuals with cardiovascular disease should exercise special caution to avoid exposure. Not for use in humans. Keep out of the reach of children. The Paylean 9 formulation (Type A Medicated Article) poses a low dust potential under usual conditions of handling and mixing. When mixing and handling Paylean, use protective clothing, impervious gloves, protective eye wear, and a NIOSH-approved dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse eyes thoroughly with water. If irritation persists, seek medical attention. The material safety data sheet contains more detailed occupational safety information. To report adverse effects, access medical information, or obtain additional product information,
call 1-800-428-4441.

Store at room temperature.
Expiration Date and Lot Number are printed on the bag. Not to be used after the expiry date.

Paylean® 9

Elanco Animal Health
A Division of Eli Lilly and Company
Indianapolis, IN 46285, U.S.A.

Questions or Comments: Call 1-800-428-4441

Exhibit II

Copy of U.S. Patent 4,690,951

United States Patent [19]

Anderson et al.

[11] **Patent Number: 4,690,951**

[45] **Date of Patent: Sep. 1, 1987**

[54] **GROWTH PROMOTION**

[75] Inventors: **David B. Anderson**, Greenfield; **Klaus K. Schmiegel**, Indianapolis; **Edward L. Veenhuizen**, Greenfield, all of Ind.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[21] Appl. No.: **811,059**

[22] Filed: **Dec. 19, 1985**

Related U.S. Application Data

[60] Division of Ser. No. 628,002, Jul. 5, 1984, abandoned, which is a continuation of Ser. No. 462,587, Jan. 31, 1983, abandoned.

[51] **Int. Cl.**[4] **A61K 31/135**

[52] **U.S. Cl.** **514/653**

[58] **Field of Search** 514/653

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,818,101	6/1974	Baile et al.	424/300
4,086,272	4/1978	Cox et al.	260/559 D
4,271,195	6/1981	Keasling	424/330
4,279,925	7/1981	Haynes	424/311
4,305,960	12/1981	Haynes	424/330
4,338,333	7/1982	Ainsworth et al.	424/309
4,391,826	7/1983	Mills et al.	424/324

FOREIGN PATENT DOCUMENTS

19241	9/1983	Australia .
0007205	1/1980	European Pat. Off. .
6735	1/1980	European Pat. Off. .
26298	4/1981	European Pat. Off. .
49728	4/1982	European Pat. Off. .
673994	3/1967	South Africa .
793295	2/1981	South Africa .
793296	2/1981	South Africa .

OTHER PUBLICATIONS

Van Dijk et al., Recueil, 92, 1281–1297 (1973).

Baker et al., Use of an Adrenergic Agonist to Alter Muscle and Fat Deposition in Lambs, *Fed. Prod.*, 42, 1983 (3069).

Ricks et al., Use of a β-Agonist to Alter Fat and Muscle Deposition in Steers, *Fed. Proc.*, 42, 1983 (3070).

Dalrymple et al., Use of the β-Agonist Clenbuterol to Alter Carcass Composition in Poultry, *Fed. Proc.*, 42, 1983 (2203).

Borsini et al., *Life Sciences*, 30, pp. 905–911 (1982).

Primary Examiner—Frederick E. Waddell

Attorney, Agent, or Firm—Charles W. Ashbrook; Leroy Whitaker

[57] **ABSTRACT**

β-Phenethanolamines are effective in promoting growth and improving feed efficiency and leanness in animals.

9 Claims, No Drawings

GROWTH PROMOTION

This is a division of Ser. No. 628,002 filed July 5,1984, now abandoned, which was a continuation of Ser. No. 462,587 filed Jan. 31, 1983, now abandoned.

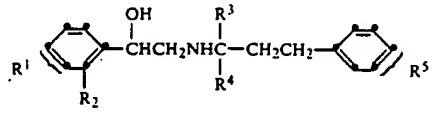
BACKGROUND OF THE INVENTION

The chemistry and use of β-phenethanolamines has been extensively investigated. A number of these compounds have been reported to have beneficial cardiac activities; see U.S. Pat. No. 3,987,200. Such compounds also are known to have sympathomimetic activity, and have found utility as utero-relaxing agents; Van Dijk et al., *Recueil*, 92, 1281 (1973). More recently, a group of β-phenethanolamines have been reported as possessing anti-hyperglycemic activity, and have been found effective in promoting the loss of weight in animals, EPO No. 6735 published Jan. 9, 1980.

An object of this invention is to provide a new use for certain β-phenethanolamines. This invention provides a method for promoting the growth of domesticated animals employing β-phenethanolamines.

SUMMARY OF THE INVENTION

This invention provides a method for increasing weight gain in animals and improving the efficiency of feed utilization and the quality of the carcass. The invention is more particularly directed to a method for promoting growth and improving feed efficiency and leanness comprising administering an effective amount of a compound having the formula



wherein:

R^1 is hydrogen, hydroxy, or methoxy;

R^2 is hydrogen or fluoro,

R^3 is hydrogen or C_1–C_2 alkyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, fluoro, nitro, hydroxy, SO_2CH_3 or $CONH_2$; provided that R^1 is hydrogen only when R^5 is nitro or SO_2CH_3; and the acid addition salts thereof.

A preferred method for promoting growth and improving feed efficency and leanness according to this invention employs a compound of the above formula wherein R^1 is hydroxy, R^2 is hydrogen, R^3 is hydrogen or methyl and R^4 is methyl. The method is most preferably practiced employing a compound wherein R^1 and R^5 both are hydroxy and R^2 and R^3 both are hydrogen and R^4 is methyl. When R^1 is hydroxy or methoxy, it preferably is in the para position. When R^5 is other than hydrogen, it also is preferably in the para position.

This invention also provides an animal feedstuff comprising a β-phenethanolamine of the above formula together with a suitable carrier therefor.

DETAILED DESCRIPTION OF THE INVENTION

The compounds employed in the method provided by this invention are either known in the art or are readily prepared by well known synthetic procedures. A particularly preferred method employs 1-(3-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]-ethanol. This β-phenethanolamine is disclosed in South African Patent No. 673,994 published in May, 1967. The most preferred embodiment of this invention employs 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamnol]ethanol, a compound disclosed as having utero-relaxing activity by Van Dijk et al. in *Recueil*, 92 1281 (1973).

The compounds to be employed in the method of this invention are readily prepared by reaction of a styrene oxide with a 3-phenylpropylamine derivative. For example, a styrene oxide such as 2-fluorostyrene oxide can be reacted with about an equimolar quantity of an amine such as 1-methyl-3-(4-nitrophenyl)propylamine in an unreactive organic solvent such as ethanol, methanol, n-propanol, dioxane, or the like. The reaction generally is carried out at a temperature of about 50° to about 120° C., and at such temperature the reaction routinely is substantially complete within about 6 to about 10 hours. The product, a β-phenethanolamine, is readily isolated by simply removing the reaction solvent, for instance by evaporation under reduced pressure, and further purification can be accomplished if desired by standard techniques, including crystallization, chromatography, acid-base extraction, and the like.

An alternative method for preparing the β-phenethanolamines to be employed in the present method comprises reacting a mandelic acid derivative with a 3-phenylpropylamine derivative to provide an amide, which upon subsequent reduction provides a compound of the above formula. For example, a phenylpropylamine derivative such as 1-methyl-3-(3-fluorophenyl)-propylamine can be reacted with an acylating agent such as a hydroxy protected mandelic acid halide, or preferably simply reacted with a mandelic acid in the presence of a common peptide coupling reagent such as N,N'-dicyclohexylcarbodiimide, carbonyldiimidazole, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, commonly referred to as EEDQ. The direct coupling reaction generally is conducted in an organic solvent such as benzene or N,N-dimethylformamide, and normally is complete after about 2 to 48 hours when carried out at about −30° to about 100° C. The product is an amide that is readily isolated by simply filtering the reaction mixture and then removing the reaction solvent. The amide thus formed is next reduced by reaction with a common reducing agent such as diborane or the like to provide a β-phenethanolamine defined by the above formula.

A similar, yet alternative, method of synthesis comprises reacting a phenethanolamine with a phenylethyl ketone to provide a Schiff base, which upon reduction gives a compound to be employed in the present method. For example, a phenethanolamine such as 2-hydroxy-2-(4-hydroxyphenyl)ethylamine can be reacted with a ketone such as methyl 2-(4-hydroxyphenyl)ethyl ketone to provide the corresponding imine, which upon reduction, for instance with 5% palladium on carbon, provides 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol.

It should be noted that the compounds to be employed in the method of this invention possess at least one asymmetric center (i.e. the carbinol center), and when R^3 and R^4 differ, the compounds possess two asymmetric centers. Since employment of individual optical isomers necessitates preparing the β-phenethanolamines from optically active starting materials, or using costly separation procedures, a preferred embodi-

ment of this invention employs a mixture of optical isomers. For example, 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol is preferably prepared from racemic mixtures of starting materials, e.g. dl-1-methyl-3-(4-hydroxyphenyl)propylamine and dl-4-hydroxystyrene oxide, to provide a mixture of all four possible optical isomers of the product. The mixture of optical isomers is employed in the method without subsequent separation of isomers.

Since the β-phenethanolamines to be employed in the present method are inherently basic, they readily form acid addition salts with any number of inorganic and organic acids. These salts can be employed in the method of the invention, and often are preferred to the free base since they generally are more soluble in solvents such as water and are more conveniently formulated as an animal feedstuff. Acids commonly employed to form acid addition salts include mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid, perchloric acid and the like; and organic acids such as acetic acid, citric acid, succinic acid, para-toluene sulfonic acid, methanesulfonic acid, lactic acid and the like. Preferred salts to be employed in the present method include the hydrochlorides and hydrobromides.

Typical β-phenethanolamines to be employed in the method of this invention include the following:

1-(3-hydroxyphenyl)-2-[1-methyl-1-ethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol;
1-(2-fluoro-4-hydroxyphenyl)-2-[1-methyl-3-(4-fluorophenyl)propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[3-(3-nitrophenyl)-propylamino]ethanol;
1-(3-hydroxy-2-fluorophenyl)-2-[3-(4-methylsulfonyl)-propylamino]ethanol;
1-(4-methoxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol;
1-phenyl-2-[1,1-dimethyl-3-(3-methylsulfonylphenyl)-propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride;
1-(phenyl)-2-[1-methyl-3-(4-nitrophenyl)-propylamino]ethanol;
1-(3-hydroxyphenyl)-2-[1-methyl-3-(4-fluorophenyl)-propylaino]ethanol succinate;
1-(4-hydroxyphenyl)-2-[1-methyl-1-ethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-phenyl-propylamino]ethanol hydrobromide; and
d-1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol.

The method of promoting growth and improving leanness and feed efficiency provided by this invention is practiced by administering an effective amount of a compound defined above to a warm-blooded animal that receives a nutritionally adequate diet. The method generally will be practiced on domesticated animals raised for human meat consumption, for example grower/finisher swine, poultry, ruminants and the like. In a preferred embodiment, the growth of pigs, chickens and turkeys is promoted employing a β-phenethanolamine. Another preferred embodiment is practiced in ruminants such as cattle, sheep and goats. The method of improving leanness is not limited to meat producing animals, and can be practiced on other warm-blooded animals, including dogs and cats. This latter embodiment is particularly useful when it is desired to maintain mature animals in a relatively lean physical state.

The method of the invention is preferably practiced by orally administering an effective amount of a β-phenethanolamine to an animal. Other routes of administration can be employed, for instance intramuscular or intravenious injection; however, such routes are less practical. The amount to be administered to an animal is an amount that is effective in causing a promotion of growth, or an improvement in the efficiency of utilization of food, or an improvement in carcass quality of the animal, for instance in the form of less fatty tissue and improved leanness. The effective amount to be administered will vary somewhat depending upon the particular animal species being treated and the particular active ingredient employed, but generally will be from about 1 to about 1000 parts per million (ppm) of total daily feed intake. Such amount will provide a dosage of about 0.05 to about 50 mg/kg. A preferred embodiment employs about 1 to about 200 ppm, and more preferably from about 5 to about 100 ppm. A typical amount of active ingredient to be administered to swine will be from about 5 to about 40 ppm. For example, when practicing the method in animals such as ruminants or swine, the compound will be added to the daily feed ration at about 5 to about 100 parts per million of the daily feed ration.

For oral administration, the active β-phenethanolamine is preferably admixed with suitable carriers or diluents commonly employed in animal husbandry. Animal feedstuffs comprising a β-phenethanolamine growth promoter as defined herein are provided as a further embodiment of this invention. Typical carriers and diluents commonly employed in such feedstuffs include corn meal, soybean meal, alfalfa meal, rice hulls, soybean mill run, cottonseed oil meal, bone meal, ground corn, corncob meal, sodium chloride, urea, cane molasses and the like. Such carriers promote a uniform distribution of the active ingredient in the finished feed ration into which such compositions are added, thereby ensuring proper distribution of the active ingredient throughout the feed. The feedstuff composition provided by the invention will contain about 5 to about 95 percent by weight of active ingredient, and more typically about 10 to about 50 percent by weight. As already noted, the acid addition salts of the active phenethanolamines are generally preferred for oral administration, and are thus the preferred form of active ingredient for the feedstuff compositions of the invention.

While the preferred method for orally administering the growth promoters is via the daily feed rations, the compounds can be incorporated into salt blocks and mineral licks, as well as being added directly to drinking water for convenient oral consumption. The compounds can additionally be formulated with polymorphous materials, waxes and the like for long-term controlled release, and administered to an animal as a bolus or tablet only as needed to maintain the desired daily payout of active ingredient.

For parenteral administration, the β-phenethanolamines can be admixed with conventional carriers such as corn oil, sesame oil, carbowax, calcium stearate and the like. Such formulations can be molded into pellets and administered as an injection or as a slowrelease subcutaneous implant. Such administrations can be made as often as needed to ensure the proper dosing of active ingredient to obtain the desired rate of growth promotion and improvement in leanness and feed efficiency.

While the compounds described herein are effective in promoting average daily weight gain and improving feed efficiency in animals, they also cause observable improvement in the quality of the meat produced. For example, the compounds appear to mobilize free fatty acids from fatty tissue and depress the deposition of fat as the animals gain weight. This reduction of fat is beneficial since the animal being treated according to the invention gains weight in the form of more useable lean meat, thereby reducing waste and improving the value of the animal thus treated. Also, mature animals that are not subject to additional weight gain can be maintained in a desirably lean form by administering a compound as described herein.

The practice of the present invention is more fully illustrated by the following detailed examples.

EXAMPLE 1

Preparation of dl-4-(benzyloxy)mandelic acid

A solution of 5.0 g of dl-4-hydroxy mandelic acid, 11.0 g of benzyl chloride and 10.0 g of potassium carbonate in 50 ml of methanol was heated to reflux and stirred for seventy-two hours. The reaction mixture was cooled to room temperature and diluted with 50 ml of water. The aqueous solution was washed twice with 50 ml portions of benzene, and then was acidified with concentrated hydrochloric acid. The aqueous acid solution was extracted three times with 50 ml portions of ethyl acetate. The organic extracts were combined, washed with water and with saturated sodium chloride solution and dried. Removal of the solvent by evaporation under reduced pressure provided 5.7 g of a solid which was then recrystallized from 300 ml of toluene to afford 5.33 g of dl-4-(benzyloxy)mandelic acid. M.P. 153°–155° C.

Analysis calc. for $C_{15}H_{14}O_4$:
Theory: C, 69.76; H, 5.46;
Found : C, 69.96; H, 5.33.

EXAMPLE 2

Resolution of dl-4-(benzyloxy)mandelic acid to provide R(−)-(4-benzyloxy)mandelic acid

To a stirred solution of 185.6 g of dl-4-benzyloxy)-mandelic acid in 2500 ml of ethyl acetate at 80° C. was added in one portion 43.6 g of R(+)-α-methylbenzylamine. The reaction mixture was cooled to room temperature, and the precipitated solid which had formed was collected by filtration and washed with fresh ethyl acetate. The solid was recrystallized twice from a solution of ninety percent ethanol in water to provide 91.4 g of the R(+)-α-methylbenzylamine salt of R(−)-4-(benzyloxy)mandelic acid. M.P. 208.5−209.5° C. $[\alpha]_D$ −38.6°, $[\alpha]_{365}$ −155.3° (MeOH)

Analysis calc. for $C_{23}H_{25}NO_4$:
Theory: C, 72.80; H, 6.64; N, 3.69;
Found : C, 72.95; H, 6.83; N, 3.95.

To a stirred suspension of 91.4 g of the above-named salt in 2000 ml of ethyl acetate was added 50 ml of ten percent aqueous hydrochloric acid solution. The aqueous acid solution was separated, and the organic layer washed with water and dried. Removal of the solvent by evaporation under reduced pressure afforded 54.5 g of R(−)-4-(benzyloxy)mandelic acid, i.e. R(−)-2-(4-benzyloxyphenyl)-2-hydroxyacetic acid. M.P. 155°–161° C. $[\alpha]_D$ −102.2°; $[\alpha]_{365}$ −410.6° (MeOH)

Analysis calc. for $C_{15}H_{14}O_4$:
Theory: C, 69.76; H, 5.46;
Found : C, 69.67; H, 5.41.

EXAMPLE 3

Preparation of dl-1-methyl-3-(4-benzyloxyphenyl)propylamine

A solution of 40.0 g of methyl 2-(4-benzyloxyphenyl-)ethyl ketone and 160 ml of anhydrous ammonia in 300 ml of ethanol was heated at 75° C. and stirred for two hours. After cooling the reaction mixture to room temperature, 4.0 g of Raney nickel was added in one portion, and the reaction mixture then was stirred at 25° C. for twelve hours under a hydrogen atmosphere at 300 psi. The reaction mixture next was filtered and the filtrate was concentrated by evaporation of the solvent under reduced pressure to provide an oil. The oil was dissolved in 120 ml of 3 N hydrochloric acid, from which the product as a hydrochloride salt precipitated. The salt so formed was collected by filtration and recrystallized from methanol and toluene to provide 36.2 g of dl-1-methyl-3-(4-benzloxyphenyl)propylaminium chloride. M.P. 195–197.5° C.

EXAMPLE 4

Resolution of dl-1-methyl-3-(4-benzyloxyphenyl)propylamine to provide R-(−)-1-methyl-3-(4-benzyloxyphenyl)propylamine

A solution of 629.3 g of dl-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride was converted to the free amine by reaction with 95 g of sodium hydroxide in 400 ml of water. The free amine was then dissolved in 2000 ml of methylene chloride and added to a solution of 328 g of D-(−)-mandelic acid in 1000 ml of methanol. The mandelic acid salt of the free amine precipitated out of solution and was recrystallized three ties from methanol to provide 322 g of the R-mandelic acid salt of R-1-methyl-3-(4-benzyloxyphenyl)propylamine. M.P. 166°–167° C. $[\alpha]_D$ −30°, $[\alpha]_{365}$ −119° (MeOH).

The salt so formed was converted to R-1-methyl-3-(4-benzyloxyphenyl)propylamine as the free base by reaction with aqueous sodium hydroxide.

EXAMPLE 5

R,R-N-[2-(4-Benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine

A solution of 93.9 g or R-1-methyl-3-(4-benzyloxyphenyl)propylamine in 500 ml of N,N-dimethylformamide containing 63.0 g of 1-hydroxybenzotriazole and 104.6 g of R-2-(4-benzyloxyphenyl)-2-hydroxyacetic acid was cooled to 0° C. and stirred while a solution of 83.6 g of N,N'-dicyclohexylcarbdiimide in 300 ml of dimethylformamide was added dropwise over one hour. The reaction mixture was stirred for twelve hours at 3° C. and then was diluted with 10 ml of water, stirred for an additional hour, and then cooled to −30° C. in an ice-acetone bath. The reaction mixture was filtered to remove dicyclohexylurea, and then the filtrate was concentrated by evaporation of the solvent under reduced pressure. The concentrated solution was diluted with ethyl acetate and washed with saturated aqueous sodium carbonate solution, with water, with 300 ml of 1N hydrochloric acid, and again with water. The organic layer was dried and the solvent was removed by evaporation under reduced pressure to provide the product as a white solid. The solid was recrystallized once from acetonitrile and again from methanol to provide 159.7 g of R,R-N-[2-(4-benzyloxyphenyl)-2-

hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)-propylamine. M.P. 145–148° C. $[\alpha]_D$ −15.9°, $[\alpha]_{365}$ −50.1° (MeOH).

Analysis calc for $C_{32}H_{33}NO_4$:
Theory: C, 77.55; H, 6.71; N, 2.83;
Found : C, 77.04; H, 6.84; N, 2.53.

EXAMPLE 6

R,R-N-[2-(4-Benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine

To a stirred solution of 10.0 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-4-benzyloxyphenyl)propylamine in 500 ml of freshly distilled tetrahydrofuran under a nitrogen gas atmosphere was added dropwise over thirty minutes 41 ml of 2 molar borane-dimethyl sulfide complex in tetrahydrofuran. The reaction mixture was stirred at 25° C. for twenty hours, and then was heated to reflux and stirred for an additional three hours. After cooling the reaction mixture to 25° C. and stirring for another eighteen hours, the excess borane was decomposed by the slow portion-wise addition or 400 ml of methanol. The solvent was then removed fro the reaction mixture by evaporation under reduced pressure to provide the product as an oil. The oil so formed was dissolved in 250 ml of hot methanol, and after concentrating the volume to 125 ml, the product began crystallizing out of solution. The crystalline product was collected by filtration and recrystallized twice from methanol to provide 6.65 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]1-methyl-3-(4-benzYloxyphenyl)propylamine. M.P. 119°–123.5° C.

The amine so formed was dissolved in methanol and added to a solution of ethereal hydrogen chloride, thereby providig 6.49 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride. M.P. 214.5–216° C. $[\alpha]_D$ −13.4°, $[\alpha]_{365}$ −30.2° (MeOH).

Analysis calc. for $C_{32}H_{36}NO_3Cl$:
Theory: C, 74.19; H, 7.00; N, 2.70; Cl, 6.84;
Found: C, 74.20; H, .98; N, 2.65; Cl, 6.63.

EXAMPLE 7

R,R-1-(4-Hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride, also name as R,R-N-[2-(4-Hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)propylaminum chloride

A mixture of 51.6 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride and 5.0 g of Raney nickel in 2 liters of ethanol and 2 liters of ethyl acetate was stirred at 25° C. for four and one-half hours under a hydrogen atmosphere of 60 psi. The reaction mixture was then filtered to remove the residual Raney nickel, and the filtrate was concentrated to an oil by evaporation of the solvent under reduced pressure, and the oil was crystallized from fresh ethanol and diethyl ether to provide 29.8 g of R,R-N-[2-(4-hydroxyphenyl)-2hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)-propylaminium chloride. M.P. 176°–176.5° C. (dec.) $[\alpha]_D$ −22.7°, $[\alpha]_{365}$ −71.2° (3.7 mg/ml MeOH).

Analysis calc. for $C_{18}H_{24}NO_3Cl$:
Theory: C, 63.99; H, 7.16; N, 4.15;
Found : C, 63.70; H, 7.26; N, 4.32.

EXAMPLE 8

As pointed out above, a preferred embodiment of this invention employs a mixture of all four optical isomers of the compound of Example 7. This racemic mixture can be prepared by the method described above by reaction of dl-4-(benzoyloxy)mandelic acid with dl-1-methyl-3-(4-benzyloxyphenyl)propylamine in the presence of DCC to give racemic 1-(4-benzyloxyphenyl)-2-oxo-2-[1-methyl-3-(4-benzyloxypnenyl)propylamino]ethanol. Reduction of the latter compound and subsequent removal of the benzyl groups provides racemic 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol. This compound is more preferably prepared by the following procedure.

A solution of 32.8 g. (0.2 m) of methyl 2-(4-hydroxyphenyl)ethyl ketone and 42.6 g. (0.2 m) of 1-(4-hydroxyphenyl)-2-aminoethanl in 380 ml. of ethanol containing 3.8 g. of five percent palladium on carbon was stirred for sixteen hours at 60° C. under hydrogen at 55 psi. The reaction mixture was then filtered, and the filtrate was diluted by addition of 350 ml. of water. The aqueous mixture was concentrated to a volume of about 400 ml., and then washed with dichloromethane. The aqueous mixture was acidified by addition of 50 ml. of conc. hydrochloric acid. After standing at room temperature for two hours, the aqueous acid mixture was filtered and the filter cake was washed with 40 ml. of ice water and dried at 50° C. in vacuum to provide 47 g. of 1-(4-hydroxyphenyl-2[1-methyl-3-4-hydroxyphenyl)-propylamino]ethanol hydrochloride. M.P. 124°–129° C.

Analysis calc. for $C_{18}H_{24}NO_3Cl$:
Theory: C, 63.99; H, 7.16; N, 4.15; Cl, 10.49.
Found: C, 63.77; H, 6.80; N, 3.91; Cl, 10.68.

^{13}C NMR studies demonstrated the product to be comprised of 51% RR,SS diastereame and 49% RS,SR diastereomer.

EXAMPLE 9

1-Phenyl-2-[1-methyl-3-(4-nitrophenyl)propylamino]ethanol

A solution of 5.0 g. (25.9 mM) of 2-amino-1-phenylethanol and 3.55 g. (25.9 mM) of methyl 2-(4-nitrophenyl)ethyl ketone in 60 ml. of toluene containing 10 mg. of para-toluenesulfonic acid was heated at reflux for six hours in a flask equipped with a Dean-Stark trap. The water that formed during the reaction was removed via the trap, and then the reaction mixture was cooled to room temperature and concentrated to dryness by evaporation of the solvent under reduced pressure. The solid product that remained was dissolved in 50 ml. of tetrahydrofuran and the solution was heated to reflux. A solution of 13.5 ml. of 2N borane-methyl sulfide complex in tetrahydrofuran was then added dropwise to the reaction mixture, and the mixture was refluxed for an additional ninety minutes. After cooling the reaction mixture to room temperature, it was diluted by addition of diethyl ether saturated with hydrogen chloride. The precipitate that formed was collected by filtration and crystallized from ethanol and diethyl ether to give 3.29 g. of 1-phenyl-2-[1-methyl-3-(4-nitrophenyl)propylamino]ethanol hydrochloride. M.P. 203°–213° C.

Analysis calc. for $C_{18}H_{23}ClN_2O_3$:
Theory: C, 61.62; H, 6.61; N, 7.98; Cl, 10.11.
Found: C, 61.76; H, 6.62; N, 7.76; Cl, 10.13.

EXAMPLE 10

1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]ethanol

A solution of 32.6 g. (0.2 m) of 1,1-dimethyl-3-phenylpropylamine and 22.9 g. (0.1 m) of 2-(4-methoxyphenyl)-2-oxoethyl bromide in 75 ml. of tetrahydrofuran was heated at reflux for thirty-six hours. The reaction mixture was then cooled and added to 2 liters of diethyl ether. The precipitate was removed by filtration, and the filtrate was acidified with hydrobromic acid to give 18.15 g. of 1-(4- methoxyphenyl)-1-oxo-2-(1,1-dimethyl-3-phenylpropylamino) ethane hydrobromide. M.P. 174°-178° C.

The compound thus formed was dissolved in 85 ml. of glacial acetic acid containing 35 ml. of hydrobromic acid, and the solution was heated at reflux for nine hours. The solution was then cooled and the solvent was removed by evaporation to provide, following crystallization from ethanol and diethyl ether, 7.8 g. of 1-(4-hydroxyphenyl)-1-oxo-2-(1,1-dimethyl-3-phenylpropylamino)ethane hydrobromide. M.P. 228°-230° C.

Catalytic hydrogenation of 5.0 g. of the compound from above in 44 ml. of ethanol containing 1.25 g. of five percent palladium on carbon afforded, following crystallization from acetone and diethyl ether, 2.3 g. of 1-(4-hydroxypheyl)-2-(1,1-dimethyl-3-phenylpropylamino)ethanol hydrobromide. M.P. 168°-170° C.

Analysis calc. for $C_{19}H_{26}BrNO_2$:
Theory: C, 60.00; H, 6.89; N, 3.68.
Found: C, 60.28; H, 6.67; N, 3.62.

EXAMPLE 11

1-(3-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethanol

To a stirred solution of 67.2 g. (0.22M) of 2-(3-benzyloxyphenyl)-2-oxoethyl bromide in 200 ml. of acetonitrile was added a solution of 54.3 g. (0.20 M) of N-benzyl-1,1-dimethyl-3-(4-fluorophenyl)propylamine in 600 ml. of acetonitrile containing 42 ml. (0.22M) of diisopropylethylamine. The reaction mixture was stirred for about six hours at reflux, and then was cooled and stored at room temperature for forty-eight hours. The reaction mixture was next diluted by addition of aqueous sodium hydroxide, and the organic solvents were removed by evaporation under reduced pressure. The aqueous alkaline mixture was extracted with ethyl acetate, which was than washed with water, dried, and concentrated to dryness to give an oil. The oil was dissolved in ethanol and diethyl ether and converted to the hydrochloride salt by addition of excess hydrogen chloride. The precipitated solid was collected by filtration and recrystallized from ethyl acetate to give 51.3 g. of 1-(3-benzyloxyphenyl)-1-oxo-2-[(N-benzyl)-1,1-dimethyl-3-(4-fluorophenyl) propylamino]ethane hydrochloride. M.P. 137°-145° C.

The compound thus prepared was reduced by reaction with 16 g. of sodium borohydride in ethanol. Isolation of the product, followed by conversion to the hydrochloride salt and crystallization from diethyl ether afforded 55.0 g. of 1-(3-benzyloxyphenyl)-2-[(N-benzyl)-1,1-dimethyl-3-(4-florophenyl)propylamino]ethanol hydrochloride. M.P. 186.5°-191° C.

A solution of 10.0 g. of the product thus produced in 200 ml. of ethanol containing 3.0 g. of Raney Nickel was shaken for two hours at 25° C. under hydrogen at 44 psi. The reaction mixture was then filtered, and the solvent was removed from the filtrate by evaporation under reduced pressure to give a white solid. The solid was triturated with ethyl acetate and air dried to provide 5.9 g. of 1-(3-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethanol hydrochloride. M.P. 196.5°-198.5° C.

Analysis calc. for $C_{19}H_{25}ClFNO_2$:
Theory: C, 64.49; H, 7.12; N, 3.96; Cl, 10.02.
Found: C, 64.29; H, 6.97; N, 4.06; Cl, 9.89.

EXAMPLE 12

1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4aminocarbonylphenyl)propylamino]ethanol

A suspension of 10.0 g. (50 mM) of 1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamine and 15.0 g. (50 mM) of 1-(4-benzyloxyphenyl)-1-oxoethyl bromide in 1000 ml. of acetonitrile containing 32.0 g. (0.3M) of sodium carbonate and 100 ml. of water was stirred for one hour at 25° C. The precipitate that formed was collected by filtration, washed with water and with diethyl ether, and air dried to provide 8.0 g. of 1-(4-benzyloxyphenyl)-1-oxo-2-[1,1-dimethyl-3(4-aminocarbonylphenyl)-propylamino]ethane. M.P. 184–187° C. This product was converted to the hydrochloride salt by reaction with hydrogen chloride in diethyl ether. M.P. 219°–224° C.

The compound thus prepared was reacted with sodium borohydride in methanol to provide, following conversion to the hydrochloride salt and crystallization from methanol and diethyl ether, 5.8 g. of 1-(4- benzyloxyphenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol hydrohloride. M.P. 141–143° C.

Reaction of the above compound with hydrogen in the presence of Raney Nickel effected cleavage of the hydroxy protecting group to afford, following crystallization of the hydrochloride salt, 1.3 g. of 1-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride. M.P. 185° C. (dec.)

Analysis calc. for $C_{22}H_{27}ClN_2O_3$:
Theory: C, 63.40; H, 7.18; N, 7.39; Cl, 9.36.
Found: C, 63.26; H, 7.01; N, 7.45; Cl, 9.42.

The compounds of Examples 13 and 14 were prepared by the general procedure of Example 12.

EXAMPLE 13

1-(2-Fluorophenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride;
M.P. 227°-230° C.

EXAMPLE 14

1-(3-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrobromide;
M.P. 161°-165° C.

EXAMPLE 15

1-Phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl)-propylamino]ethanol hydrochloride

Methyl 2-(4-methylthiophenyl)ethyl ketone was oxidized by reaction with m-chloroperbenzoic acid to give methyl 2-(4-methylsulfonylphenyl)ethyl ketone. A solution of 6.73 g. of 2-amino-1-phenylethanol and 1.10 g. of methyl 2-(4-methylsufonylphenyl)ethyl ketone in 500 ml. of toluene containing 200 mg. of p-toluenesulfonic acid was heated at reflux for twenty-four hours. The reaction mixture was cooled and the solvent was removed by evaporation to give the Schiff base 1-phenyl-

2-[1-methyl-3-(4-methylsulfonylphenyl)propylimino]ethanol. The Schiff base thus prepared was reacted with 3.7 g. of sodium borohydride in 500 ml. of ethanol at 0° C. for sixteen hours. The reaction mixture was diluted by addition of 50 ml. of acetone and 20 ml. of 3N hydrochloric acid. The mixture was concentrated to an oil by evaporation of the solvent. The oil crystallized upon standing at room temperature. Recrystallization of the product from 200 ml. of hot ethanol afforded 8.96 g. (48% yield) of 1-phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl)propylamino]ethanol hydrochloride. M.P. 164°–170° C.

Analysis calc. for $C_{19}H_{26}ClNO_3S$:

Theory: C, 59.44; H, 6.83; N, 3.65; Cl, 9.23; S, 8.35.

Found: C, 59.28; H, 6.57; N, 3.70; Cl, 9.36; S,8.11.

EXAMPLE 16

Premix for Chickens

Ingredient	% by weight
1-(4-hydroxyphenyl)-2-[1.1-dimethyl-3-phenylpropylamino]-ethanol succinate	25
Ground Corn	74
Sodium Chloride	1
	100

EXAMPLE 17

Premix for ruminants

Ingredient	% by weight
1-(2-fluorophenyl)-2-[1.1-dimethyl-3-(4-aminocarbonyl-phenyl)propylamino]ethanol	30
Ground yellow corn	60
Alfalfa meal	10
	100

EXAMPLE 18

Premix for Swine

Ingredient	% by weight
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol hydrochloride	10
Soybean mill run	88
Mineral oil	2
	100

The above ingredients are blended to uniformity to provide a dry flowable premix that can be admixed with a typical animal feed ration at a rate to provide about 20 ppm of active ingredient in the final feed ration. For example, the premix can be added to the following swine grower ration for covenient oral administration of the β-phenethanolamine to swine.

Ingredient	% by weight	lbs/Ton
Corn, yellow, ground	76.70	1534
Soybean Oil Meal, solvent extracted, dehulled	19.35	387
Calcium Carbonate	1.20	24
Dicalcium Phosphate, feed grade	1.20	24
Salt (sodium chloride)	0.50	10
Trace mineral premix, AN-03[1]	0.10	2
Swine Vitamin Premix, SW-03[2]	0.65	13
Vitamin A Premix, 3M USP units/lb.[3]	0.05	1
Methionine Hydroxy Analogue, 93%	0.20	4
Selenium Premix[4]	0.005	1
	100.00	2000

[1]Each Kg of premix contains: 50 g. manganese as manganese sulfate; 100 g. zinc as zinc carbonate; 50 g. iron as ferrous sulfate; 5 g. copper as copper oxide; 1.5 g. iodine as potassium iodide and 150 g. maximum and 130 g. minimum calcium as calcium carbonate.

[2]Each Kg of premix contains: 77,161 IU Vitamin D_3; 2,205 IU Vitamin E; 411 mg. riboflavin; 1,620 mg. pantothenic acid; 2,205 mg. niacin; 4.4 mg. Vitamin B_{12}; 441 mg. Vitamin K; 19,180 mg. choline; 110 mg. folic acid; 165 mg. pyridoxine; 110 mg. thiamine; 22 mg. biotin.

[3]Each Kg of premix contains 6,613,800 IU Vitamin A.

[4]Each Kg of premix contains 200 mg. of selenium as sodium selenite.

EXAMPLE 19

Feed Ration for Lambs

Ingredient	Percent	lbs/T
Yellow corn	61.00	1220.0
Corn cobs	20.00	400.0
Alfalfa Meal, dehydrated	5.40	108.0
Soybean oil meal	8.00	160.0
Urea, feed grade	0.50	10.0
Molasses, cane	3.00	60.0
Dicalcium phosphate	0.43	8.6
Salt	0.30	6.0
Calcium carbonate	0.14	2.3
Trace mineral premix[1]	0.03	0.6
Vitamin A + D_3 Premix[2]	0.10	2.0
Vitamin E Premix[3]	0.10	2.0
1-(4-Hydroxyphenyl)-2-(1.1-dimethyl-3-phenylpropylamino)-ethanol	1.00	20.0
	100.00	2000.0

[1]Trace mineral premix contains: 2.5% manganese as manganese oxide, 0.07% iodine as potassium iodide, 0.3% cobalt as cobalt carbonate, 0.5% copper as copper oxide, and 20.0% zinc as zinc sulfate.

[2]Each pound of vitamin A and D_3 premix contains 2,000,000 USP units Vitamin A and 225,750 USP units Vitamin D_3.

[3]Each pound of Vitamin E premix contains 20,000 IU Vitamin E.

The compounds to be employed in the method of this invention have demonstrated efficacy in animal tests designed to establish beneficial nutritional effects. In one test designed to show lipolytic activity, normal swine, either barrows or gilts, were employed to analyze the effect of compounds on blood glucose, insulin, and non-esterifed fatty acids (NEFA).

Test animals were maintained in metabolism crates, and following a period of adaptation, catheters were placed in their femoral veins. Prior to administration of the test compounds, all animals were fasted for a period of forty hours. Such fasting causes an elevation of NEFA's in the blood. On the day of the test, all animals were fed a norml feed ration, and one group of animals were held as controls while another group of animals received a test compound. The test compounds were administered at 200 mcg/kg intravenously, or orally at 1 mg/kg. Blood samples were taken from each animal immediately prior to treatment and then at one hour intervals fo a period of six hours following treatment. The blood plasma was analyzed for glucose, insulin and NEFA content.

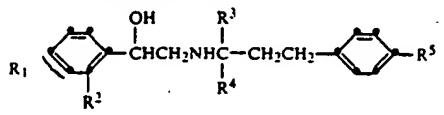
When the fasted pigs were fed the normal feed ration without a test compound, the NEFA levels in the blood drop dramatically and remained low. A β-phenethanolamine as defined herein cased either an elevation in NEFA's, or inhibited the drop in NEFA's. Blood

levels of glucose and insulin were also elevated with the β-phenethanolamines.

The following Table presents the lipolytic activity of several preferred β-phenethanolamines when evaluated according to the test described above. The results are averages of several tests.

TABLE I

Lipolytic Activity (increase in NEFA's)



R^1	R^2	R^3	R^4	R^5	% increase in NEFA's over control	% increase in glucose over control
H	H	H	CH_3	SO_2CH_3	131	9
p-OH	H	CH_3	CH_3	H	445	48
m-OH	H	CH_3	CH_3	H	71	31
m-OH	H	CH_3	CH_3	F	28	72
p-OH	H	CH_3	CH_3	OH	141	35
p-OH	H	CH_3	CH_3	$CONH_2$	18	169
m-OH	H	CH_3	CH_3	OH	68	40
H	H	H	H	NO_2	199	7
p-OCH_3	H	CH_3	CH_3	H	84	25
p-OCH_3	H	CH_3	CH_3	OH	249	5
H	H	H	CH_3	NO_2	1458	27

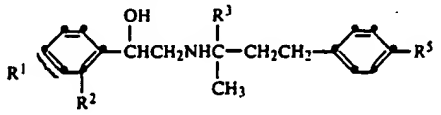
A ten day in vivo study was employed to determine the effect of β-phenethanolamines on feed efficiency and rate of growth. In these studies, barrows and gilts weighing approximately 60 kg were maintained in individual pens. Each treatment was replicated six times in randomly assigned animals, with each test animal forming an experimental unit. A group of control animals received a noral swine grower feed ration comprising the following igredients:

Ingredient	% by weight
Ground yellow corn	76.70
Soybean oil meal	19.35
Calcium carbonate	1.20
Dicalcium phosphate	1.20
Salt	0.50
Trace mineral premix	0.10
Swine Vitamin premix	0.65
Vitamin A premix, 3M USP units/lb.	0.05
Methionine Hydroxy analogue, 93%	0.20
Selenium premix	0.05
	100.00

The test animals received the same feed ration plus the test compound. All animals received feed and water ad libitum. All animals were weighed on day 1 and again on day 10, and feed consumption as measured by recording all feed issued and any remaining feed on day 10. The results of two series of this 10 day test for several β-phenethanolamines are given in Table II. In the Table, the column labelled "ADG" is the average daily weight gain in pounds; "ADF" is the average daily feed consumption (in pounds) by the test animals; and F/G is the feed efficiency calculated as ADF divided by ADG.

TABLE II

Growth Promotion and Feed Efficiency



R^1	R^2	R^3	R^5	dose ppm	ADG	ADF	F/G
			Experiment I				
Control					1.60	4.7	2.98
p-OH	H	H	OH	20	2.19	5.0	2.33
H	H	H	NO_2	20	1.78	4.22	2.37
			Experiment II				
Control					1.34	4.16	3.22
p-OH	H	CH_3	H	20	1.60	4.26	2.66
m-OH	H	CH_3	F	20	1.52	4.57	3.01

The β-phenethanolamines to be employed in the method of this invention can be administered in combination with other compounds known to have a beneficial effect upon animals. Typical compounds to be coadministered with the β-phenethanolamines include antibiotics, for example any of the tetracyclines, tylosin, penicillins, cephalosporins, polyether antibiotics, glycopeptides, orthosomycins and related compounds commonly administered to swine, poultry, ruminants and the like. A preferred combination to be employed in the present method is an antibiotic such as tylosin or a tetracycline, together with 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxypnenyl)propylamino]ethanol. Such combinations will comprise the respective components in a ratio of about 1 to about 2 parts by weight of β-phenethanolamine and about 1 to about 10 parts by weight of the partner component.

In a typical treatment, 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol was evaluated in a 42-day study employing finishing swine. Each treatment was replicated four times, with three pigs per replication. All treatments included a normal feed diet plus tylosin at 40 g/T. The animals were tested for growth performance and feed efficiency enhancement. Carcass quality was determined by analysis for fat and muscling. The results of the study are given in Table III. Both β-phenethanolamine treatments resulted in improved growth performance and carcasses with less fat and more muscle.

TABLE III

Growth Promotion, Feed Efficiency and Carcass Quality

	β-phenethanolamine[2]				
	Control[1]	20 g/T	% change	40 g/T	% change
ADG	1.94	2.07	(6.7)	2.05	(5.7)
ADF	6.28	6.63	(5.6)	6.64	(5.7)
F/G	3.24	3.20	(−1.2)	3.24	(0)
Live Wt. at Slaughter, lb	217.0	223.0	(2.8)	221.0	(1.8)
Chilled Carcass Wt., lb	154.6	160.5	(3.8)	159.8	(3.4)
Fat Depth at 10th Rib, in	1.15	1.09	(−5.2)	1.05	(−8.7)
Loin Eye Area Sp., in	4.64	4.91	(5.8)	4.84	(4.3)
Estimated pounds of Fat Free Muscle[3]	74.2	78.8	(6.1)	78.4	(5.7)

[1]all diets contained 40 g/T of tylosin
[2]1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol hydrochloride
[3]A regression equation was employed in arriving at the numerical predictions of carcass muscle (J. Animal Science, 1977, Vol. 44:8-17).

The data reported in Table III further demonstrates that the β-phenethanolamines described herein promote growth, improve feed efficiency and improve leaness.

In a similar study conducted over a 61 day period, a group of control animals received a normal daily feed ration with no additive. Another group of animals received the feed ration plus tylosin at 40 g/T, while another group received the feed ration plus 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride (compound A) at 20 g/T. A final group of finishing swine received the feed ration plus the combination of 40 g/T of tylosin and 20 g/T of the phenethanolamine. The results of this trial are given in Table IV.

TABLE IV

	Control	Tylosin	A	Tylosin + A
ADG	1.63	1.64	1.36	1.50
ADF	5.64	5.77	5.10	5.38
F/G	3.46	3.51	3.77	3.59
Slaughter Wt. (lbs)	210	211	193	201
Carcass Wt. (lbs)	150.3	151.5	140.1	146.3
Fat Depth. 10th rib. (in)[1]	0.96	0.96	0.80	0.85
Loin Eye Area (in^2)[1]	4.60	4.68	4.92	5.00
Est. % Muscle[2]	49.2	49.2	51.4	51.2
Est. Pounds Muscle[2]	75.3	76.5	74.1	76.8

[1]These results are based upon measurement of fat at the 10th rib after the carcass is split in half across the backbone.
[2]A regression equation is employed in arriving at the numerical predictions of carcass muscle (J. Animal Science, 1977, Vol. 44:8-17).

As in the previous study, both phenethanolamine treatments resulted in carcasses with less fat and more muscle. It should also be noted that the estimated amount of carcass muscle produced with the Tylosin +A treatment was similar to that produced in the control and the Tylosin treatment alone. This result was achieved, however, with less feed consumption than either the control or the Tylosin treatments.

Additional studies have been carried out to demonstrate the anabolic effect of β-phenethanolamines in swine. The effect of the compounds on nitrogen retention in finishing barrows was determined. Nitrogen retention is the difference between nitrogen intake and nitrogen excreted. Increased nitrogen retention is known to be associated with increased anabolic activity, resulting in improved carcass muscling and leanness.

In a typical study, barrows weighing about 172 pounds (78 Kg) were orally administered various doses of 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride (Compound A). All animals received water and a constant amount of normal swine feed ration. The results of this study are presented in Table V, and show that all β-phenethanolamine treatments improved nitrogen retention compared to controls.

TABLE V

Treatment	Nitrogen Retention Animals per treatment	Nitrogen Retained (g/day)
Control	6	21.0
Compound A (5 g/T)	3	23.6
Compound A (10 g/T)	3	23.9
Compound A (20 g/T)	3	25.0

As pointed out above, the method of this invention can be practiced with individual isomers of β-phenethanolamines or with mixtures of isomers and diastereomers. In a study to determine the effect on weight gain and feed efficacy of various mixtures of diastereomers, barrows initially weighing about 177 pounds were fed a normal swine diet plus a β-phenethanolamine at 20 g/T of feedstuff. Each treatment was replicated in twelve individually fed animals. The results are presented in Table VI and show that growth performance was improved by both β-phenethanolamine treatments with very little change in feed intake.

TABLE VI

Treatment	Average Daily Feed (lbs)	Average Daily Gain (lbs)
Control	5.89	1.58
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylámino]ethanol hydrochloride 57.5% RR.SS 42.5% RS.SR	5.94	2.15
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride 47% RR.SS 53% RS.SR	5.86	1.95

The data in Table VI demonstrates that the method of improving feed efficiency and promoting growth can be practiced with any desired mixture of β-phenethanolamine optical isomers.

The efficacy of the β-phenethanolamines described herein also has been demonstrate in poultry. In a typical study, broilers, that were twenty-one days old were administered an oral dosing of a β-phenethanolamine in their normal daily feed ration. All animals received the following broiler finisher ration:

Ingredients	% by weight	lbs/T
Ground yellow corn	66.40	1328.00
Animal-vegetable fat	1.53	30.60
Corn Glut. meal (60%)	4.00	80.00
Soybean meal (48%)	19.19	383.80
Fish meal-menhaden	2.50	50.00
Dicalcium phosphate	1.01	34.20
Feather meal-Hydr.	2.50	50.00
Ground limestone	0.83	16.60
Salt	0.30	6.00
Vitamin Premix[1]	0.50	10.00
Trace mineral premix[2]	0.10	2.00
Methionine Hyd. Anal.	0.15	3.00
Lysine HCl	0.29	5.80
	100.00	2000.00

[1]Vitamin premix provides 3000 IU of vitamin A, 900 ICU of vitamin D_3, 40 mg. of vitamin E, 0.7 mg. of vitamin K, 1000 mg of choline, 70 mg. of niacin, 4 mg of pantothenic acid, 4 mg of riboflavin, 100 mcg of vitamin B_{12}, 100 mcg of biotin and 125 mg of ethoxyquin per kg of complete feed.
[2]Trace mineral premix provides 75 mg of manganese, 50 mg of zinc, 25 mg of iron and 1 mg of iodine per kg of complete feed.

Test animals received with the above ration varying doses of 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride (compound A). Each treatment was replicated sixteen times, and the test was terminated when the animals reached fifty-six days of age. The animals were analyzed for weight gain and feed efficiency. The results of this test in broilers is presented in Table VII as mean weight gain and mean feed to gain ratios.

TABLE VII

Growth Performance of Broilers					
		Weight Gain		Feed Efficiency	
Treatment	Dose (g/T)	grams	% improvement	Feed/ Gain Ratio	% change from control
Control		1473	0	2.336	0
Compound A	10	1585	7.6	2.292	1.9
Compound A	20	1613	9.5	2.298	1.6
Compound A	40	1550	5.2	2.312	1.0
Compound A	80	1669	13.3	2.221	4.9

The results of this study demonstrate that the β-phenethanolamines described herein are effective in promoting growth and improving feed efficiency in poultry.

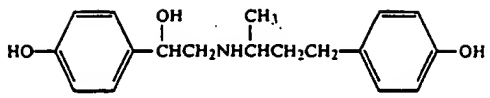
The compounds of the invention also have demonstrated efficacy in ruminants. Forty-eight crossbred wether lambs were employed in a test designed to show the effects of Compound A (1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride) at varying doses. Sixteen animals were held as controls, while sixteen received 40 ppm of Compound A, and another sixteen received 80 ppm of Compound A. All animals received a normal daily feed ration and water ad libitum. Average daily weight gain and average daily feed consumption after twenty-eight days is given below in Table VIII. The data demonstrates that a β-phenethanolamine as defined herein is effective in promoting growth and improving feed efficiency in ruminants.

TABLE VIII

Growth Performance of Lambs				
Treatment	Dose (ppm)	ADG (lbs)	ADF (lbs)	F/G
Control	0	0.414	3.68	8.89
Compound A	40	0.418	3.61	8.64
Compound A	80	0.472	3.57	7.56

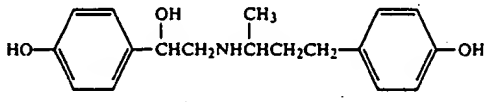
We claim:

1. A method for promoting the growth of a ruminant comprising administering to the ruminant a growth promoting amount of a compound of the formula



or an acid addition salt thereof.

2. A method for improving the efficiency of feed utilization by ruminants comprising administering to the ruminant an effective amount of a compound of the formula



or an acid addition salt thereof.

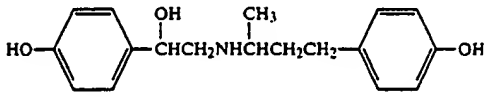
3. The method of claim 1 employing 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride.

4. The method of claim 1 employing R,R-1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol, or an acid addition salt thereof.

5. The method of claim 2 employing 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride.

6. The method of claim 2 employing R,R-1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol, or an acid addition salt thereof.

7. A method for improving leanness in domesticated animals comprising administering to the anixal an effective amount of a compound of the formula



or an acid addition salt thereof.

8. The method of claim 7 employing 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride.

9. The method of claim 7 employing R,R-1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol, or an acid addition salt thereof.

* * * * *

Exhibit III

Certificate of Correction

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,690,951

DATED : September 1, 1987

INVENTOR(S) : D. B. Anderson, K. K. Schmiegel, E. L. Veenhuizen

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below: On the title page Item (75)

Add as Inventor -- Ronald R. Tuttle --.

Column 2, line 5, "(4-hydroxyphenyl)-propylamnol]" should be -- (4-hydroxyphenyl)-propylamino] --.

Column 5, line 59, "50 ml" should be -- 150 ml --.

Column 6, line 36, "ties" should be -- times --; and line 52, "dicyclohexylcarbdiimide" should be -- dicyclohexylcarbodiimide --.

Column 7, line 24, "fro" should be -- from --; line 43, "H, .98" should be -- H, 6.98 --; and line 50, "yl-3-(4-hydroxyphenyl)propylaminum" should be -- yl-3-(4-hydroxyphenyl)propylaminium --.

Column 8, line 31, "hydroxyphenyl-2[1-methyl-3-4-hydroxyphenyl)-" should be -- hydroxyphenyl-2-[1-methyl-3-(4-hydroxyphenyl)- --.

Column 9, line 27, "1-(4-hydroxypheyl)-2-(1,1-dimethyl-3-phenyl-" should be -- 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-phenyl- --; and line 48, "than" should be -- then --; and line 62, "zyl)-1,1-dimethyl-3-(4-florophenyl)-propylamino]e-" should be -- zyl)-1,1-dimethyl-3-(4-fluorophenyl)-propylamino]e- --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,690,951

DATED : September 1, 1987

INVENTOR(S) : D. B. Anderson, K. K. Schmiegel, E. L. Veenhuizen

It is certified that error appears in the above—identified patent and that said Letters Patent is hereby corrected as shown below:

Column 10, line 11, "1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4aminocar-" should be — 1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-aminocar- --; line 22, "1-oxo-2-[1,1-dimethyl-3(4-aminocarbonylphenyl)-" should be — 1-oxo-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)- —; and line 63, "1.10 g." should be — 11.10 g. --.

Column 12, line 67, "cased" should be — caused —.

Column 18, claim 7, line 33, "anixal" should be — animal --.

Signed and Sealed this

Twenty-second Day of November, 1988

Attest:

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks

Exhibit IV

Maintenance Fee Receipt

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000139

M75N4

ELI LILLY & COMPANY
ATTENTION: PATENT DIVISION/PFEE
LILLY CORPORATE CENTER
INDIANAPOLIS IN 46285

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,690,951	185	2910	----	06/811,059	09/01/87	12/19/85	12	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	X-5683B

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231**

☆ U.S. GPO: 1998-437-690/79138

Exhibit V

Letter Transmitting INAD to FDA

Elanco Regulatory Services
Elanco Products Company
A Division of Eli Lilly and Company

740 South Alabama Street
Indianapolis, Indiana 46285
Telephone (317) 261-3221

ELANCO

April 23, 1984

Lonnie Luther, Ph.D.
Group Leader Swine and Poultry Production Drugs
Group, HFV-128
Division of Biometrics and Production
Drugs
Center for Veterinary Medicine
Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Luther:

Re: INAD Request - Notice of Claimed Investigational Exemption for a New Animal Drug - Phenethanolamine

Elanco Products Company wishes to request an INAD number for this compound in order to establish a file in the FDA. Further data will need to be compiled before a slaughter authorization will be requested.

Sincerely,

ELANCO PRODUCTS COMPANY

Signed

S. E. Poe, Ph.D.
Product Registration Manager
Animal Products Regulatory Services

SEP:djr

Exhibit VI

Copy of FDA Letter Acknowledging Receipt
and Assigning INAD No. 4231

MAY 14 1984

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

May 9, 1984

INAD-4231

Stanley E. Poe, Ph.D.
Product Registration Manager
Animal Products Regulatory Services
Elanco Products Company
A Division of Eli Lilly and Company
740 South Alabama Street
Indianapolis, Indiana 46285

Dear Dr. Poe

We acknowledge receipt of your submission dated April 23, 1984 which pertains to the investigational use of Phenethalolamine.

Your submission has been assigned INAD number 4231, and is being forwarded to the proper reviewer for consideration.

Please refer to this number when submitting any future correspondence which pertains to the use of the aforementioned drug.

This is not an authorization letter.

Sincerely yours,

Signed

Edward H. Ross, Acting Supervisor
Document Control Staff
Center for Veter9inary Medicine

Exhibit VII

Letter Transmitting NADA to fDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

NEW ANIMAL DRUG APPLICATION
(Drugs for Animal Use)
(Title 21, CFR 514)

Form Approved; OMB No. 0910-0032
Expiration Date: December 31, 1988

NADA _____

GENERIC NAME:
Ractopamine Hydrochloride

PROPRIETARY NAME
PAYLEAN™

TYPE OF SUBMISSION *(Check one)*

- [x] ORIGINAL APPLICATION *(CFR 514.1(a))*
- [ ] AMENDMENT TO AN UNAPPROVED ORIGINAL APPLICATION *(CFR 514.6)*
- [ ] SUPPLEMENT TO AN APPROVED APPLICATION *(CFR 514.8(a))*
- [ ] AMENDMENT TO AN UNAPPROVED SUPPLEMENT TO AN APPROVED APPLICATION *(CFR 514.6)*
- [ ] SPECIAL SUPPLEMENT TO AN APPROVED APPLICATION - CHANGES BEING EFFECTED *(CFR 514.8 (a))*

NAME OF APPLICANT
Elanco Products Company
Division of Eli Lilly and Company

ADDRESS *(Street Number, City, and Zip Code)*
Lilly Corporate Center
Indianapolis, IN 46285

No new animal drug application may be processed unless a completed application form has been received (21 CFR 514.1)

INSTRUCTIONS FOR PREPARING AND SUBMITTING THE NEW ANIMAL DRUG APPLICATION

i. Assemble and bind three identical copies of the submission.

ii. Identify each front cover with the name of the applicant, the proprietary name, if available, the name of the new animal drug and the dosage form.

iii. Use separate pages for each numbered heading consistent with subparagraph (1) through (12) of this application form. **Number the pages of the new animal drug application**. Each copy should bear the same page numbering.

iv. Each copy of an original new animal drug application shall contain three complete sets of labeling.

v. Submit separate applications for each different dosage form of the drug proposed. Repeating in each application basic information pertinent to all dosage forms is unnecessary if reference is made to the application containing such information. Such references should be made by volume and page. Include in each application information applicable to the specific dosage form, such as, labeling, composition, stability data, efficacy data, method of manufacture and investigational new animal drug application number.

vi. Forward amendments, supplements, reports and other correspondence submitted after the original application in the above format. Identify the submission with the assigned NADA number. If the submission is a supplemental application, full information shall be provided on each proposed change concerning any statement made in the approved application.

[NOTE: Only this front page need be submitted with additional or supplemental information.]

vii. Submit to: **Food and Drug Administration**
Center for Veterinary Medicine
(HFV-16)
5600 Fishers Lane
Rockville, MD 20857

The undersigned official submits this application for a new animal drug pursuant to section 512(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that the labeling and advertising for the new animal drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application and if the article is a prescription new animal drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the new animal drug will also contain, in the same language and emphasis, information for its use including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions contained in the labeling which is part of this application in accordance with 21 CFR 201.105. It is understood that all representations in this application apply to the drug produced until changes are made in conformity with 21 CFR 514.8. It is further understood that new animal drugs as defined in 21 CFR 510.3, intended for use in the manufacture of animal feeds in any State will be shipped only to persons who may receive such drugs in accordance with 21 CFR 510.7.

The official agent by signing below certifies, that the methods, facilities, and controls described under item 5 of this application conform to the appropriate section of the current good manufacturing practice regulations in 21 CFR PART 200.

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

SIGNATURE OF RESPONSIBLE OFFICIAL OR AUTHORIZED AGENT
Stanley E. Tole

DATE RECEIVED:

TITLE OF AUTHORITY
Product Registration Manager

DATE OF APPLICATION
August 27, 1987

FOR FDA USE ONLY

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant does not have a place of business within the United States, the application must also provide the name and address of and be countersigned by an authorized agent or official residing or maintaining a place of business within the United States

FORM FDA 356V (7/86) PREVIOUS EDITIONS ARE OBSOLETE

1. IDENTIFICATION

DATE: August 27, 1987

ORIGINAL APPLICATION:

21 CFR 514
Subpart A, §514.1

NAME OF APPLICANT:	ADDRESS:
Elanco Products Company Division Eli Lilly and Company	Lilly Corporate Center Indianapolis, IN 46285

CHEMICAL NAME:

DL-4-hydroxy-•[[[3-(4-hydroxyphenyl)-1-methylpropyl]amino]methyl]benzenemethanol, hydrochloride

GENERIC NAME:

Ractopamine Hydrochloride

PROPRIETARY NAME:

Paylean™

Exhibit VIII

FDA Letter Acknowledging Receipt

SEP 9 1987

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Rockville MD 20857

September 1, 1987

NADA 140-863

Stanley E. Poe, Ph.D.
Elanco Products Company
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Poe

We acknowledge receipt of your submission dated August 27, 1987 which pertains to a New Animal Drug Application for Ractopamine Hydrochloride for in swine.

Your submission has been assigned NADA number 140-863 and is being forwarded to the proper reviewer for consideration.

Please refer to this number when submitting any future correspondence which pertains to the use of the aforementioned drug in this species.

This is not an authorization letter.

Sincerely yours,

Signed

Doriel J. Christensen, Supervisor
Document Control Staff
Center for Veter9inary Medicine

Exhibit IX

FDA Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DEC 22 1999

NADA 140-863, E0076

Bruce W. Martin, DVM, Ph.D.
Manager, Animal Science Regulatory Affairs
Elanco Animal Health
2001 W. Main Street
P.O. Box 708
Greenfield, IN 46140

Dear Dr. Martin:

We refer to your letter dated October 8, 1999, which reactivated your original new animal drug application on (NADA 140-863) for the use of ractopamine hydrochloride in finishing swine feeds. We also refer to your letters dated October 12, November 3, and December 12, 1999, that contained final Copies of the Type A medicated article label and Type B and C medicated feed labels as well as the missing pages from your environmental assessment and corrected patent information. These submissions fulfill the requirements for approval of your original NADA for ractopamine hydrochloride (Paylean®) in finishing swine.

We have completed our review of your new animal drug application and find that it supports the approval of ractopamine hydrochloride (Paylean®) in finishing swine for increased rate of weight gain, improved feed efficiency, and increased carcass leanness when fed at 4.5 g ractopamine hydrochloride/ton of feed when swine are fed a complete ration containing at least 16% crude protein from 150 lb (68 kg) to 240 lb (109 kg) body weight, and for improved feed efficiency and increased carcass leanness when fed at 4.5 to 18 g ractopamine hydrochloride/ton of feed when swine are fed a complete ration containing at least 16% crude protein from 150 lb (68 kg) to 240 lb (109 kg) body weight. Further, a zero-day withdrawal period is approved for the indications listed above. A copy of the Freedom of Information Summary is enclosed for your files.

The application is approved as of the date of this letter. You may initiate distribution and marketing of this product upon completion of manufacturing process validation and after submitting three (3) copies of each component of the final printed labeling (FPL).

The FPL should be submitted under separate cover directly to:

Document Control Unit (UFV- 199)
Attention: HFV- 120
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

RECEIVED DEC 13 1999

The stability data submitted with this application supports a 24 months expiration date for the Paylean® Type A medicated article. A 24 months expiration date should be placed on the labeling for the drug product. Labeling must be identical to the labeling submitted in your application.

Although the completion of manufacturing process validation is not a requirement for pre-approval, it is a cGMP requirement that must be met before any shipments of drug product are made. Manufacturing process validation is based on the documented successful evaluation of multiple full scale batches (usually a minimum of three (3)) and provides assurance that the processes will reliably meet predetermined specifications. This information may have been available for evaluation by the FDA District Office during the pre-approval inspection and may have been found acceptable, However, if this information was not available at that time or process validation deficiencies were noted by the FDA Investigator during the pre-approval inspection, the appropriate FDA District Office should be contacted after manufacturing process validation has been completed and prior to shipment of the drug product. This will provide (he FDA District Office the opportunity to inspect and verify the validation of the manufacturing process. Regulatory action, such as seizure, will be considered in instances where there is shipment of the drug product prior to completion of the process validation.

Under section 512(cX2)(F)(i) of the FFDCA, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

Future correspondence regarding this approval should reference the correspondence date of this submission and our file number, NADA 140-863, E0076. Any request to change the conditions of the original approval for this NADA will be considered a supplement to your original NADA.

Sincerely yours,

signed

Stephen F. Sundlof, DVM, Ph.D.
Director, Center for Veterinary Medicine

Enclosure (FOI Summary)

Exhibit X

Description of Significant Activities

Ractopamine hydrochloride
INAD / NADA
Correspondence Chronology

Date // Code	From	RE:	Technical Section
4/23/84	**Elanco**	**Request for establishing INAD file**	**Efficacy**
5/3/84	Elanco	Protocol for residue study	Residue
5/9/84 // INAD 4231	**CVM**	**Acknowledge receipt of 5/7/84 request for INAD & assign INAD number 4231**	**Efficacy**
6/7/84 // INAD 4231	Elanco	Protocol for acute toxicology study	HHSafety
7/2/84 // INAD 4231	CVM	Protocol for acute toxicology study	HHSafety
7/16/84 // INAD 4231	CVM	Protocol for residue study	Residue
7/19/84 // INAD 4231	Elanco	Request for meeting	HHSafety
8/13/84 // INAD 4231	Elanco	Protocol: swine reproductive safety study	TASS
8/13/84 // INAD 4231	Elanco	Protocol: residue depletion study	Residue
8/27/84 // INAD 4231	Elanco	Request for meeting on 9/13/84	HHSafety
9/20/84 // INAD 4231	CVM	8/13/84 Protocol	TASS
11/23/84 // INAD 4231	CVM	8/13/84 Protocol	Residue
12/21/84 // INAD 4231	Elanco	Reports: threshold assessment evaluation:	HHSafety
1/17/85 // INAD 4231	**Elanco**	**Request for slaughter authorization**	**HHSafety**
1/30/85 // INAD 4231	Elanco	Protocol: clinical efficacy	Efficacy
2/21/85 // INAD 4231	Elanco	Additional tox info	HHSafety
3/14/85 // INAD 4231	Elanco	Protocols: TAS and tolerance studies	TASS
4/4/85 // INAD 4231	Elanco	Tox study report	HHSafety
4/11/85 // INAD 4231	Elanco	Protocol: tox study	HHSafety
4/15/85 // INAD 4231	CVM	Slaughter authorization	HHSafety; Residue
5/16/85 // INAD 4231	Elanco	Protocols: stability studies	CM&C
5/29/85 // INAD 4231	CVM	Response: Protocol	Efficacy
6/7/85 // INAD 4231	CVM	Response: Protocols for stability studies	CM&C
6/13/85 // INAD 4231	Elanco	Protocol for tox study:	HHSafety
6/13/85 // INAD 4231	Elanco	Reports: residue studies	Residue
6/25/85 // INAD 4231	CVM	Protocol for TAS and tolerance study	TASS
7/10/85 // INAD 4231	CVM	4/11/85 tox Protocol	HHSafety
7/12/85 // INAD 4231	CVM	tox studies for threshold assessment	HHSafety
8/23/85 // INAD 4231	**Elanco**	**Submission: first (NCIE)**	**Efficacy**
8/28/85 // INAD 4231	CVM	Protocol for tox study	HHSafety
10/17/85 // INAD 4231	Elanco	Protocol has been modified	Efficacy
12/19/85 // INAD 4231	Elanco	Protocol: Efficacy study	Efficacy
12/19/85 // INAD 4231	Elanco	Environmental testing plan	EA
2/13/86 // INAD 4231	Elanco	Tox Study outline	HHSafety
2/25/86 // INAD 4231	CVM	Protocol is OK	Efficacy
3/18/86 // INAD 4231	CVM	Ractopamine is non-gentoxic	HHSafety
3/19/86 // INAD 4231	CVM	12/19/85 Protocol	Efficacy
3/25/86 // INAD 4231	CVM	2/13/86 Study outline	HHSafety
4/2/86 // INAD 4231	CVM	12/19/85 Environmental testing	EA
4/10/86 // INAD 4231	Elanco	Published paper	HHSafety
6/12/86 // INAD 4231	Elanco	Protocol: radiolabeled tissue residue study	Residue
8/14/86 // INAD 4231	Elanco	Statistical evaluation of clinical data	Efficacy

8/27/86 // INAD 4231	CVM	Radiolabeled tissue residue study protocol	Residue
8/28/86 // INAD 4231	Elanco	Environmental fate package	EA
10/29/86 // INAD 4231	Elanco	Radiolabeled tissue residue study protocol	Residue
11/6/86 // INAD 4231	CVM	Statistical evaluation of clinical data	Efficacy
11/20/86 // INAD 4231	CVM	8/28/86 Environmental fate	EA
12/19/86 // INAD 4231	Elanco	Additional environmental study reports	EA
1/7/87 // INAD 4231	Elanco	Balance-Excretion Study	Residue
1/22/87 // INAD 4231	Elanco	Protocol: clinical efficacy	Efficacy
1/28/87 // INAD 4231	CVM	Residue study protocol	Residue
1/29/87 // INAD 4231	Elanco	Comparative metabolism	Residue
2/19/87 // INAD 4231	CVM	Balance-Excretion Study	Residue
3/23/87 // INAD 4231	CVM	Comparative metabolism	Residue
3/23/87 // INAD 4231	CVM	Clinical efficacy protocol	Efficacy
3/23/87 // INAD 4231	CVM	Environmental study reports	EA
3/31/87 // INAD 4231	Elanco	Lab animal bioavailability studies	HHSafety
4/22/87 // INAD 4231	Elanco	Residue study	Residue
4/30/87 // INAD 4231	Elanco	Clinical protocol	Efficacy
5/14/87 // INAD 4231	Elanco	Tissue Residue Study	Residue
5/15/87 // INAD 4231	CVM	Request for slaughter authorization	Efficacy
5/28/87 // INAD 4231	Elanco	Bioavailability study report	Efficacy
6/4/87 // INAD 4231	Elanco	Reports of corroborative efficacy studies:	Efficacy
7/15/87 // INAD 4231	CVM	Bioavailability studies	HHSafety
7/15/87 // INAD 4231	CVM	Residue studies	Residue
8/27/87 // Original NADA	**Elanco**	**Original NADA,**	**ALL**
9/1/87 // NADA 140-863	**CVM**	**Acknowledge receipt of 8/27/87 original NADA, assigned number 140-863**	**ALL**
9/14/87 // INAD 4231	CVM	Bioavailability study	Efficacy
10/1/87 // NADA 140-863	Elanco	VMF assigned for bulk drug mnfg.	CM&C
10/21/87 // INAD 4231	CVM	Slaughter Authorization	Efficacy
12/1/87//NADA 140-863	Elanco	Reproductive safety in swine protocol	TASS
2/5/88 // INAD 4231	Elanco	Request for add'l slaughter authorization	Residue
3/18/88 // NADA 140-863	**CVM**	**Response: 8/27/87 original application -**	**ALL**
3/18/88 // INAD 4231	CVM	Repro safety Protocol	TASS
4/22/88	CVM	Slaughter Authorization	Efficacy
6/2/88 // NADA 140-863	Elanco	Revised label	Label
6/2/88 // NADA 140-863	Elanco	Summary report of three efficacy trials	Efficacy
8/11/88 // NADA 140-863	Elanco	Target Animal Safety section	TASS
8/18/88 // NADA 140-863	Elanco	M&C and Labeling	Label
8/30/88 // NADA 140-863	Elanco	Revised labeling	Label
9/15/88 // NADA 140-863	Elanco	EA studies	EA
10/27/88 // NADA 140-863	Elanco	Stability study	CM&C
10/27/88 // NADA 140-863	Elanco	EA studies	EA
10/28/88 // NADA 140-863	CVM	Worker safety study	EA
10/28/88 // NADA 140-863	CVM	protocol	EA
11/22/88 // NADA 140-863	Elanco	TASS data	TASS
11/28/88 // NADA 140-863	Elanco	Revised FOI summary	FOI
11/30/88 // NADA 140-863	Elanco	Manufacturing	CM&C
12/1/88 // NADA 140-863	Elanco	Feed Stability Protocols	CM&C
12/1/88 // NADA 140-863	Elanco	Bag specifications	CM&C
12/1/88 // NADA 140-863	Elanco	Statistical summaries of clinical data	Efficacy
12/15/88 // NADA 140-863	Elanco	Statistical summaries of clinical data	Efficacy
12/15/88 // NADA 140-863	Elanco	Patent info	Patent
12/19/88 // NADA 140-863	CVM	Clinical data	Efficacy
1/2/89 // NADA 140-863	Elanco	EA study	EA
1/9/89 // INAD 4231	CVM	Slaughter Authorization	Efficacy
1/11/89	CVM	Stability protocols	CM&C

1/24/89 // NADA 14-863;	Elanco	Manufacturing	CM&C
2/2/89 // NADA 140-863	Elanco	Updated labeling	Label
2/9/89 // NADA 140-863	Elanco	Tox study	EA
2/16/89 // NADA 140-863	Elanco	Tox study	TASS
2/28/89 // NADA 140-863	CVM	M&C and labeling	Label
3/2/89 // NADA 140-863	Elanco	EA information	EA
3/2/89 // NADA 140-863	Elanco	EA information	EA
3/2/89 // NADA 140-863	Elanco	Revised complete EA	EA
4/3/89 // NADA 140-863	CVM	Manufacturing	CM&C
4/3/89 // NADA 140-863	CVM	Partial response to 8/11/88 submission	TASS
4/3/89 // NADA 140-863	CVM	Efficacy evaluation	Efficacy
4/3/89 // NADA 140-863	**CVM**	**"... ractopamine does not have to meet section 558.15 criteria."**	**Microbio Safety**
4/3/89 // NADA 140-863	CVM	FOI evaluation	FOI
4/4/89 // NADA 140-863	CVM	Approving 1/24/89 M&C submission	CM&C
4/6/89 // NADA 140-863	CVM	Approving 11/30/88 M&C submission	CM&C
4/14/89 // NADA 140-863	CVM	Response	various
5/25/89 // NADA 140-863	Elanco	Acknowledge 4/14/89 letter	Residue
6/8/89 // NADA 140-863	Elanco	Partial response to 4/3/89 letter	TASS; Effic
7/17/89 // NADA 140-863	CVM	Response: 2/16/89 submission	TASS
8/9/89 // NADA 140-863	Elanco	Completion of response to 4/3/89 letter	TASS; Effic
8/9/89 // NADA 140-863	Elanco	Response to 7/17/89 letter	TASS
9/14/89 // NADA 140-863	Elanco	Swine feed assay method	Feed Method
10/12/89 // NADA 140-863	Elanco	INAD trial report	Efficacy
10/31/89 // NADA 140-863	CVM	Response to 2/2/89 submission	various
12/13/89 // NADA 140-863	Elanco	INAD trial report	Efficacy
1/11/90 // NADA 140-863	Elanco	Efficacy discussion	Efficacy
2/28/90 // NADA 140-863	CVM	Response: 8/9/89 submission	TASS
3/1/90 // NADA 140-863	Elanco	Response: 10/31/89 letter	various
3/8/90 // NADA 140-863	CVM	Method is ready for method trial	Feed Method
3/12/90 // NADA 140-863	CVM	Efficacy discussion	Label; Effic
5/9/90 // NADA 140-863	CVM	Tox studies	HHSafety
5/24/90 // NADA 140-863	Elanco	Tox summary	HHSafety
6/18/90 // NADA 140-863	Elanco	TASS data	TASS
7/19/90 // NADA 140-863	Elanco	Two residue protocols	Residue
8/20/90 // NADA 140-863	CVM	Residue protocols	Residue
9/5/90 // INAD 4231	CVM	Slaughter Authorization	Residue
9/13/90 // NADA 140-863	Elanco	Residue protocol	Residue
10/18/90 // NADA 140-863	Elanco	Protocol: efficacy trials	Efficacy
11/8/90 // NADA 140-863	CVM	Residue protocol	Residue
1/7/91 // NADA 140-863	Elanco	Residue protocol	Residue
1/17/91 // NADA 140-863	CVM	Laboratory trial of the feed method	Feed Method
1/22/91 // NADA 140-863	CVM	Tox studies	HHSafety
2/13/91 // NADA 140-863	Elanco	Data from batches of medicated feed	Feed Method
3/5/91 // NADA 140-863	Elanco	Additional patent information	Patent
3/12/91 // NADA 140-863	CVM	Efficacy protocol	Efficacy
4/8/91 // NADA 140-863	Elanco	Feed samples	Feed Method
4/12/91 // NADA 140-863	Elanco	Summary of residue data	Residue
5/10/91 // INAD 4231	Elanco	Efficacy protocols, proposed label	Label; Effic
5/30/91 // INAD 4231	Elanco	Revised efficacy protocols	Efficacy
6/28/91 // NADA 140-863	Elanco	Tissue residue studies	Residue
7/1/91 // INAD 004-231	CVM	Efficacy protocol	Efficacy
7/11/91 // NADA 140-863	Elanco	Tissue Residue Studies	Residue
7/22/91 // INAD 004-231	CVM	Revised efficacy protocols	Efficacy
7/29/91 // NADA 140-863	CVM	Residue section status	Residue
7/30/91 // INAD 4231	Elanco	Efficacy protocol	Efficacy

7/30/91 // NADA 140-863	CVM	Swine feed assay method	Feed Method
9/10/91 // INAD 4231	Elanco	Efficacy study protocol	Efficacy
9/10/91 // NADA 140-863	Elanco	Tissue residue studies	Residue
9/11/91 // INAD 4231	Elanco	Revised efficacy study protocol	Efficacy
9/16/91 // NADA 140-863	CVM	Non-pivotal efficacy studies	Efficacy
9/19/91 // NADA 140-863	CVM	Residue Studies	Residue
9/25/91 // NADA 140-863	Elanco	Residue data	Residue
10/7/91 // NADA 140-863	CVM	Tissue Residue	Residue
11/4/91 // INAD 004-231	CVM	Efficacy study protocol	Efficacy
11/4/91 // INAD 004-231	CVM	Efficacy study protocol	Efficacy
11/14/91 // NADA 140-863	Elanco	Tox data	HHSafety
11/15/91 // NADA 140-863	Elanco	Tox data	HHSafety
2/21/92 // NADA 140-863	CVM	Tox data	HHSafety
3/12/92 // INAD 004-231	CVM	Efficacy studies	Efficacy
3/17/92 // INAD 4231	Elanco	Protocol: tox study	HHSafety
4/14/92 // NADA 140-863	Elanco	Response: tox data	HHSafety
4/15/92 // INAD 4231	Elanco	Request for add'l slaughter authorization	Residue
7/1/92 // INAD 004-231	CVM	Protocol: tox study	HHSafety
7/24/92 // NADA 140-863	Elanco	Tox data	HHSafety
8/4/92 // INAD 004-231	CVM	Slaughter authorization	Efficacy
12/22/92 // NADA 140-863	CVM	Response: several submissions	various
1/11/93 // NADA 140-863	Elanco	Two tissue residue analytical methods	Tissue Method
3/3/93 // INAD 4231	Elanco	Protocol: Toxicity Study	HHSafety
4/27/93 // INAD 004-231	CVM	Protocol: Toxicity Study	HHSafety
5/21/93 // NADA 140-863	CVM	Response to several sections	various
7/6/93 // INAD 4231	Elanco	Revised protocol for tox study	HHSafety
7/7/93 // NADA 140-863	Elanco	Response: Feed Method data	Feed Method
8/12/93 // NADA 140-863	Elanco	Status request	TASS
9/16/93 // NADA 140-863	CVM	Sponsor Monitored Method Trial	Feed Method
9/30/93 // INAD 4231	Elanco	Updated and complete EA	EA
10/7/93 // INAD 004-231	CVM	7/6/93 protocol	HHSafety
10/7/93 // INAD 4231	Elanco	Tox study reports	HHSafety
10/21/93 // NADA 140-863	Elanco	Manufacture of bulk drug	CM&C
10/22/93 // INAD 4231	Elanco	Data	HHSafety
10/22/93 // NADA 140-863	Elanco	Manufacture of Type A Medicated Article	CM&C
11/3/93 // INAD 4231	Elanco	Updated efficacy section	Efficacy
11/4/93 // INAD 4231	Elanco	Patent information, labeling, and FOI summary	Label, FOI,Pat
2/1/94 // INAD (T) 004-231	CVM	**Target animal safety section is complete**	TASS
3/4/94 // NADA 140-863	Elanco	Feed method and validation	Feed Method
3/8/94 // NADA 140-863	Elanco	Data	Tissue Method
3/14/94 // INAD (H) 004-231	CVM	Tox data	HHSafety
3/16/94 // NADA 140-863	CVM	Manufacturing & EA	CM&C; EA
4/14/94 // NADA 140-863	Elanco	Amendment to feed method	Feed Method
4/20/94 // NADA 140-863	CVM	Feed Method protocol	Feed Method
4/22/94 // NADA 140-863	Elanco	Amendment to feed method	Feed Method
4/29/94 // N-140-863	CVM	Feed method	Feed Method
5/13/94 // INAD 4231	Elanco	Tox data	HHSafety
5/16/94 // NADA 140-863	CVM	Desk review has begun	Tissue Method
5/19/94 // INAD 4231	Elanco	Amendment to the patent information	Patent
8/4/94 // NADA 140-863	Elanco	Revised protocol	Feed Method
8/10/94 // N-140863	CVM	Method Trial	Tissue Method
8/18/94 // INAD (Z) 004-231	CVM	EA	EA
8/25/94 // N-140863	CVM	Revised Protocol	Feed Method
9/30/94 // INAD (E) 004-231	CVM	Effectiveness data are acceptable, dose rage of 5-20 ppm is accepted for F/G and Carcass claims with 5-day w/d	Label CM&C; Efficacy; FOI

10/05/94 // INAD (H) 4-231	CVM	Tox data, NOEL	HHSafety
11/7/94 // NADA 140-863	Elanco	Response: 9/21/94 letter	CM&C
11/14/94 // NADA 140-863	Elanco	Sponsor Monitored Method Trial	Feed Method
11/15/94 // NADA 140-863	Elanco	Regulatory method trials	Tissue Method
1/6/95 // NADA 140-863	Elanco	Update of patent information	Patent
1/18/95 // INAD 4231	Elanco	Summary report of tox study	HHSafety
2/3/95 // N-140863	CVM	Method trial	Tissue Method
2/15/95 // V005182-C-004	CVM	Manufacturing	CM&C
2/21/95 // INAD 4231	Elanco	Final report tox study	HHSafety
2/28/95 // N-140863	CVM	Sponsor monitored feed method trial	Feed Method
3/7/95 // N-140863-G-0064	CVM	Response: 11/7/94 submission	CM&C
3/9/95 // NADA 140-863	Elanco	Pelleted swine feed stability study	Label, CM&C
3/10/95 // NADA 140-863	Elanco	Revised procedures for tissue residues	Tissue Method
3/22/95 // NADA 140-863	Elanco	Revised feed method trial protocol	Feed Method
4/25/95 // INAD 4231	Elanco	VMF	CM&C
4/27/95 // NADA 140-863	Elanco	Request PAI	CM&C
5/2/95 // INAD 4231	Elanco	VMF	HHSafety
5/4/95 // INAD 4231	Elanco	Updated and complete EA	EA
5/5/95 // INAD 4231	Elanco	Pivotal clinical trial data analysis	Efficacy
5/11/95 // INAD 4231	Elanco	TASS data	TASS
5/16/95 // N-140863	CVM	Laboratory phase of the method trial	Feed Method
6/1/95 // INAD 4231	Elanco	TASS data	TASS
6/5/95 // INAD 4231	Elanco	Residue data	Residue
6/8/95 // NADA 140-863	Elanco	Update of patent information	Patent
7/17/95 // I-004231	CVM	Pelleting stability	Label, CM&C
7/17/95 // I-004231	CVM	Method for ractopamine in feed	Feed Method
8/2/95 // INAD 4231	Elanco	Method trial & revised analytical method	Feed Method
8/22/95 // INAD 4231	CVM	**0-day w/d is acceptable**	Residue
8/23/95 // I-004231	CVM	Sponsor Monitored Method Trial	Tissue Method
9/22/95 // INAD 4231	CVM	**Safe tissue concentrations of 0.25 ppm (muscle), 0.75 ppm (liver), 1.5 ppm (kidney or fat)**	HHSafety; Residue
10/16/95 // NADA 140-863	Elanco	Update of patent information	Patent
10/23/95 // INAD 4231	Elanco	Revised methods	Tissue Method
10/24/95 // INAD 4231	Elanco	Sponsor Monitored Method Trial Protocol	Tissue Method
10/25/95 // I-004231	CVM	**Analytical Method for Feed approved, regulatory limits in feed set at 80 to 110% of label claim**	Feed Method
10/25/95 // Z 004231	CVM	EA	EA
11/15/95 // I-0042310	CVM	Sponsor Monitored Method Trial Protocol	Tissue Method
11/15/95 // I-004231	CVM	Method trial	Tissue Method
11/21/95 // E 004-231	CVM	**effectiveness data (performance, carcass) are acceptable, dose rage of 5-20 ppm is accepted for F/G and Carcass claims with 0-day w/d - effectiveness component is complete**	Label; Efficacy
11/27/95 // INAD 4231	Elanco	Updated environmental assessment	EA
12/6/95 // T 004-231	CVM	**Target animal safety section is complete**	TASS
12/7/95 // INAD 4231	Elanco	Sponsor Monitored Method Trial Protocol	Tissue Method
1/19/96 // I-004231	CVM	Sponsor Monitored Method Trial Protocol	Tissue Method
1/25/96 // INAD 4231	Elanco	Confirmatory Method Trial Protocol	Tissue Method
2/19/96 // INAD 4231	Elanco	Determinative Method Trial Protocol	Tissue Method
2/20/96 // I-004231	CVM	Confirmatory Method Trial Protocol	Tissue Method
3/5/96 // I-004231	CVM	Determinative Tissue Residue Method	Tissue Method
3/8/96 // V-005182	CVM	bulk drug manufacturing	CM&C
4/17/96 // V-005477	CVM	**Limits for Type A Med Article are 85 – 105% of labeled claim or NLT 7.7 g/lb (17 g/kg) and NMT 10.5 g/lb (21 g/kg).**	CM&C

6/3/96 // I-004231	CVM	**EA technical section complete**	EA
7/12/96 // INAD 4231	CVM	tox study	HHSafety
9/12/96 // INAD 4231	Elanco	Confirmatory Method Trial & Method	Tissue Method
9/17/96 // INAD 4231	Elanco	Determinative Method Trial & Method	Tissue Method
10/22/96 // I-004231	CVM	**Confirmatory Method is acceptable**	Tissue Method
12/13/96 // INAD 4231	Elanco	Tox data	HHSafety
12/16/96 // I-004231	CVM	**Determinative method is acceptable at 6 ppb and above.**	Tissue Method
12/17/96 // INAD 4231	Elanco	FOI and Labeling	Label
12/18/96 // INAD 4231	Elanco	Reactivate Efficacy Technical Section	Efficacy
1/22/97 // VMF 5477	Elanco	Stability data and proposed expiry dating	CM&C
6/2/97 // INAD 4231	Elanco	Technical Section complete letter	CM&C
6/20/97 // VMF 005-477	CVM	**VMF is complete, and 24 months expiration dating on Type A Article approved**	CM&C
7/30/97//INAD 004321	CVM	Tox data	HHSafety
8/11/97// INAD 4231	Elanco	Protocols for tox studies	HHSafety
8/12/97//INAD 4231	CVM	Technical section status	CM&C
1/16/98//INAD 004-231	CVM	Label claim	Label; Effic
2/25/98//INAD 4231	Elanco	Tox data	HHSafety
2/26/98//INAD 4231	Elanco	Label claim	Label; Effic
2/26/98//INAD 004-231	CVM	FOI and Labeling	Label; FOI
3/10/98//INAD 4231	Elanco	Tox data	HHSafety
6/2/98//INAD 004231	CVM	Tox data	HHSafety
7/9/98 // INAD	Elanco	Proposed swine muscle tolerance	Residue
9/9/98// INAD 4231	CVM	Safe concentration is set at 0.25 ppm in muscle and the **muscle tolerance is set at 50 ppb parent ractopamine.**	Tissue Method; Residue
10/27/98//INAD 4231	Elanco	Tox data	HHSafety
11/12/98//INAD 004-231	CVM	**Effectiveness Technical Section complete**	Label; Effic
11/19/98 // INAD 4231	Elanco	Tox data	HHSafety
12/11/98//INAD 4231	Elanco	C,M & C Technical Section status	CM&C
12/14/98//INAD 4231	Elanco	Validated muscle tissue methods	Tissue Method
12/17/98 // INAD 4231	Elanco	Updated FOI	FOI
2/17/99 // INAD 4231	Elanco	Updated FOI	FOI
2/18/99 // INAD 4231	Elanco	Labels	Label
3/26/99//INAD 004-231	CVM	**C,M & C technical section is complete.**	CM&C
04/08/99 // INAD 4231	Elanco	Camera-ready paper and electronic copy of EA	EA
5/24/99 // INAD 4231	CVM	**Human Health Safety Technical Section Complete.** Liver tolerance of parent compound is 0.150 ppm and for muscle is 0.05 ppm. **No withdrawal period is required in swine.**	HHSafety
6/17/99 // INAD 4231	CVM	Tox data	HHSafety
7/09/99 // INAD 4231	CVM	**Environmental Assessment technical section complete letter. FONSI attached.**	EA
9/27/99//INAD 4231	CVM	**Methods are acceptable for both Muscle and Liver tissues, therefore residue technical section is complete.**	Tissue Method
10/06/99 // INAD 004-231	CVM	**Freedom of Information technical section complete ; Labeling Technical Section Complete.**	Label; FOI
10/8/99 // NADA 140-863	Elanco	Administrative NADA	ALL
10/12/99 // NADA 140-863	Elanco	1st Amendment to Admin NADA – amended Type B&C labels	Label
11/3/99 // NADA 140-863	Elanco	2nd Amendment to Admin NADA – amended Type A&B labels	Label
12/12/99 // NADA 140-863	Elanco	3rd Amendment to Admin NADA – amended EA	EA; Patent

12/22/99 // NADA 140-863	CVM	and patent info Approval to market Paylean	ALL

Exhibit XI

U.S. Patent 4,734,437

United States Patent [19]

Anderson et al.

[11] **Patent Number: 4,734,437**

[45] **Date of Patent: * Mar. 29, 1988**

[54] **GROWTH PROMOTION**

[75] Inventors: **David B. Anderson**, Greenfield; **Klaus K. Schmiegel**, Indianapolis; **Edward L. Veenhuizen**, Greenfield, all of Ind.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[*] Notice: The portion of the term of this patent subsequent to Sep. 1, 2004 has been disclaimed.

[21] Appl. No.: **860,719**

[22] Filed: **May 7, 1986**

Related U.S. Application Data

[63] Continuation of Ser. No. 628,002, Jul. 5, 1984, abandoned, which is a continuation of Ser. No. 462,587, Jan. 31, 1983, abandoned.

[51] **Int. Cl.**[4] **A61K 31/135**

[52] **U.S. Cl.** **514/653**

[58] **Field of Search** 514/653

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,818,101	6/1974	Baile et al.	424/300
4,271,195	6/1981	Keasling	424/330

FOREIGN PATENT DOCUMENTS

67/3994 3/1967 South Africa .

OTHER PUBLICATIONS

Baker et al., Use of an adrenergic agonist to alter muscle and fat deposition in lambs, *Fed. Prod.*, 42,1983 (3069).

Ricks et al., Use of a β-agonist to alter fat and muscle deposition in steers, *Fed. Proc., 42,* 1983 (3070).

Dalrymple et al., Use of the β-agonist clenbuterol to alter carcass composition in poultry, *Fed. Proc., 42,* 1983 (2203).

Borsini et al., *Life Sciences, 30,* pp. 905–911 (1982).

Primary Examiner—Frederick E. Waddell

Attorney, Agent, or Firm—Charles W. Ashbrook; Leroy Whitaker

[57] **ABSTRACT**

β-Phenethanolamines are effective in promoting growth and improving feed efficiency and leanness in animals.

8 Claims, No Drawings

GROWTH PROMOTION

This application is a continuation of application Ser. No. 628,002, filed July 5, 1984, now abandoned which was a continuation of Ser. No. 462,587 filed Jan. 31, 1983, now abandoned.

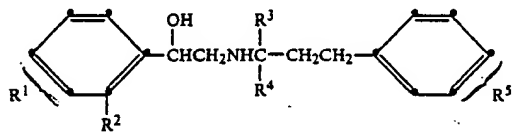
BACKGROUND OF THE INVENTION

The chemistry and use of β-phenethanolamines has been extensively investigated. A number of these compounds have been reported to have beneficial cardiac activities; see U.S. Pat. No. 3,987,200. Such compounds also are known to have sympathomimetic activity, and have found utility as utero-relaxing agents; Van Dijk et al., *Recueil*, 92, 1281 (1973). More recently, a group of β-phenethanolamines have been reported as possessing anti-hyperglycemic activity, and have been found effective in promoting the loss of weight in animals, EPO No. 6735 published January 9, 1980.

An object of this invention is to provide a new use for certain β-phenethanolamines. This invention provides a method for promoting the growth of domesticated animals employing β-phenethanolamines.

SUMMARY OF THE INVENTION

This invention provides a method for increasing weight gain in animals and improving the efficiency of feed utilization and the quality of the carcass. The invention is more particularly directed to a method for promoting growth and improving feed efficiency and leanness comprising administering an effective amount of a compound having the formula



wherein:

R^1 is hydrogen, hydroxy, or methoxy;

R^2 is hydrogen or fluoro,

R^3 is hydrogen or C_1–C_2 alkyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, fluoro, nitro, hydroxy, SO_2CH_3 or $CONH_2$; provided that R^1 is hydrogen only when R^5 is nitro or SO_2CH_3; and the acid addition salts thereof.

A preferred method for promoting growth and improving feed efficency and leanness according to this invention employs a compound of the above formula wherein R^1 is hydroxy, R^2 is hydrogen, R^3 is hydrogen or methyl and R^4 is methyl. The method is most preferably practiced employing a compound wherein R^1 and R^5 both are hydroxy and R^2 and R^3 both are hydrogen and R^4 is methyl. When R^1 is hydroxy or methoxy, it preferably is in the para position. When R^5 is other than hydrogen, it also is preferably in the para position.

This invention also provides an animal feedstuff comprising a β-phenethanolamine of the above formula together with a suitable carrier therefor.

DETAILED DESCRIPTION OF THE INVENTION

The compounds employed in the method provided by this invention are either known in the art or are readily prepared by well known synthetic procedures. A particularly preferred method employs 1-(3-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol. This β-phenethanolamine is disclosed in South African Patent No. 673,994 published in May, 1967. The most preferred embodiment of this invention employs 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol, a compound disclosed as having utero-relaxing activity by Van Dijk et al. in *Recueil*, 92 1281 (1973).

The compounds to be employed in the method of this invention are readily prepared by reaction of a styrene oxide with a 3-phenylpropylamine derivative. For example, a styrene oxide such as 2-fluorostyrene oxide can be reacted with about an equimolar quantity of an amine such as 1-methyl-3-(4-nitrophenyl)propylamine in an unreactive organic solvent such as ethanol, methanol, n-propanol, dioxane, or the like. The reaction generally is carried out at a temperature of about 50° to about 120° C., and at such temperature the reaction routinely is substantially complete within about 6 to about 10 hours. The product, a β-phenethanolamine, is readily isolated by simply removing the reaction solvent, for instance by evaporation under reduced pressure, and further purification can be accomplished if desired by standard techniques, including crystallization, chromatography, acid-base extraction, and the like. 5 An alternative method for preparing the β-phenethanolamines to be employed in the present method comprises reacting a mandelic acid derivative with a 3-phenylpropylamine derivative to provide an amide, which upon subsequent reduction provides a compound of the above formula. For example, a phenylpropylamine derivative such as 1-methyl-3-(3-fluorophenyl)propylamine can be reacted with an acylating agent such as a hydroxy protected mandelic acid halide, or preferably simply reacted with a mandelic acid in the presence of a common peptide coupling reagent such as N,N'-dicyclohexylcarbodiimide, carbonyldiimidazole, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, commonly referred to as EEDQ. The direct coupling reaction generally is conducted in an organic solvent such as benzene or N,N-dimethylformamide, and normally is complete after about 2 to 48 hours when carried out at about −30° to about 100° C. The product is an amide that is readily isolated by simply filtering the reaction mixture and then removing the reaction solvent. The amide thus formed is next reduced by reaction with a common reducing agent such as diborane or the like to provide a β-phenethanolamine defined by the above formula.

A similar, yet alternative, method of synthesis comprises reacting a phenethanolamine with a phenylethyl ketone to provide a Schiff base, which upon reduction gives a compound to be employed in the present method. For example, a phenethanolamine such as 2-hydroxy-2-(4-hydroxyphenyl)ethylamine can be reacted with a ketone such as methyl 2-(4-hydroxyphenyl)ethyl ketone to provide the corresponding imine, which upon reduction, for instance with 5% palladium on carbon, provides 1-(4-hydroxyphenyl)-2-[1-methyl-3(4-hydroxyphenyl)propylamino]ethanol.

It should be noted that the compounds to be employed in the method of this invention possess at least one asymmetric center (i.e. the carbinol center), and when R^3 and R^4 differ, the compounds possess two asymmetric centers. Since employment of individual optical isomers necessitates preparing the β-phenethanolamines from optically active starting materials, or

using costly separation procedures, a preferred embodiment of this invention employs a mixture of optical isomers. For example, 1-(4-hydroxyphenyl)2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol is preferably prepared from racemic mixtures of starting materials, e.g. dl-1-methyl-3-(4-hydroxyphenyl)propylamine and dl-4-hydroxystyrene oxide, to provide a mixture of all four possible optical isomers of the product. The mixture of optical isomers is employed in the method without subsequent separation of isomers.

Since the β-phenethanolamines to be employed in the present method are inherently basic, they readily form acid addition salts with any number of inorganic and organic acids. These salts can be employed in the method of the invention, and often are preferred to the free base since they generally are more soluble in solvents such as water and are more conveniently formulated as an animal feedstuff. Acids commonly employed to form acid addition salts include mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid, perchloric acid and the like; and organic acids such as acetic acid, citric acid, succinic acid, para-toluene sulfonic acid, methanesulfonic acid, lactic acid and the like. Preferred salts to be employed in the present method include the hydrochlorides and hydrobromides.

Typical β-phenethanolamines to be employed in the method of this invention include the following:

1-(3-hydroxyphenyl)-2-[1-methyl-1-ethyl-3-(4aminocarbonylphenyl)propylamino]ethanol;
1-(2-fluoro-4-hydroxyphenyl)-2-[1-methyl-3-(4fluorophenyl)propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[3-(3-nitrophenyl)propylamino]ethanol;
1-(3-hydroxy-2-fluorophenyl)-2-[3-(4-methylsulfonyl)propylamino]ethanol;
1-(4-methoxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol;
1-phenyl-2-[1,1-dimethyl-3-(3-methylsulfonylphenyl)propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-(4- -hydroxyphenyl)propylamino]ethanol hydrochloride;
1-(phenyl)-2-[1-methyl-3-(4-nitrophenyl)propylamino]ethanol;
1-(3-hydroxyphenyl)-2-[1-methyl-3-(4-fluorophenyl)propylamino]ethanol succinate;

1-(4-hydroxyphenyl)-2-[1-methyl-1-ethyl-3(4-aminocarbonylphenyl)propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]ethanol hydrobromide; and
d-1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3(4-hydroxyphenyl)propylamino]ethanol.

The method of promoting growth and improving leanness and feed efficiency provided by this invention is practiced by administering an effective amount of a compound defined above to a warm-blooded animal that receives a nutritionally adequate diet. The method generally will be practiced on domesticated animals raised for human meat consumption, for example grower/finisher swine, poultry, ruminants and the like. In a preferred embodiment, the growth of pigs, chickens and turkeys is promoted employing a β-phenethanolamine. Another preferred embodiment is practiced in ruminants such as cattle, sheep and goats. The method of improving leanness is not limited to meat producing animals, and can be practiced on other warm-blooded animals, including dogs and cats. This latter embodiment is particularly useful when it is desired to maintain mature animals in a relatively lean physical state.

The method of the invention is preferably practiced by orally administering an effective amount of a β-phenethanolamine to an animal. Other routes of administration can be employed, for instance intramuscular or intravenious injection; however, such routes are less practical. The amount to be administered to an animal is an amount that is effective in causing a promotion of growth, or an improvement in the efficiency of utilization of food, or an improvement in carcass quality of the animal, for instance in the form of less fatty tissue and improved leanness. The effective amount to be administered will vary somewhat depending upon the particular animal species being treated and the particular active ingredient employed, but generally will be from about 1 to about 1000 parts per million (ppm) of total daily feed intake. Such amount will provide a dosage of about 0.05 to about 50 mg/kg. A preferred embodiment employs about 1 to about 200 ppm, and more preferably from about 5 to about 100 ppm. A typical amount of active ingredient to be administered to swine will be from about 5 to about 40 ppm. For example, when practicing the method in animals such as ruminants or swine, the compound will be added to the daily feed ration at about 5 to about 100 parts per million of the daily feed ration.

For oral administration, the active β-phenethanolamine is preferably admixed with suitable carriers or diluents commonly employed in animal husbandry. Animal feedstuffs comprising a β-phenethanolamine growth promoter as defined herein are provided as a further embodiment of this invention. Typical carriers and diluents commonly employed in such feedstuffs include corn meal, soybean meal, alfalfa meal, rice hulls, soybean mill run, cottonseed oil meal, bone meal, ground corn, corncob meal, sodium chloride, urea, cane molasses and the like. Such carriers promote a uniform distribution of the active ingredient in the finished feed ration into which such compositions are added, thereby ensuring proper distribution of the active ingredient throughout the feed. The feedstuff composition provided by the invention will contain about 5 to about 95 percent by weight of active ingredient, and more typically about 10 to about 50 percent by weight. As already noted, the acid addition salts of the active phenethanolamines are generally preferred for oral administration, and are thus the preferred form of active ingredient for the feedstuff compositions of the invention.

While the preferred method for orally administering the growth promoters is via the daily feed rations, the compounds can be incorporated into salt blocks and mineral licks, as well as being added directly to drinking water for convenient oral consumption. The compounds can additionally be formulated with pólymorphous materials, waxes and the like for long-term controlled release, and administered to an animal as a bolus or tablet only as needed to maintain the desired daily payout of active ingredient.

For parenteral administration, the 3-phenethanolamines can be admixed with conventional carriers such as corn oil, sesame oil, carbowax, calcium stearate and the like. Such formulations can be molded into pellets and administered as an injection or as a slow-release subcutaneous implant. Such administrations can be made as often as needed to ensure the proper dosing of active ingredient to obtain the desired rate of growth

promotion and improvement in leanness and feed efficiency.

While the compounds described herein are effective in promoting average daily weight gain and improving feed efficiency in animals, they also cause observable improvement in the quality of the meat produced. For example, the compounds appear to mobilize free fatty acids from fatty tissue and depress the deposition of fat as the animals gain weight. This reduction of fat is beneficial since the animal being treated according to the invention gains weight in the form of more useable lean meat, thereby reducing waste and improving the value of the animal thus treated. Also, mature animals that are not subject to additional weight gain can be maintained in a desirably lean form by administering a compound as described herein.

The practice of the present invention is more fully illustrated by the following detailed examples.

EXAMPLE 1

Preparation of dl-4-(benzyloxy)mandelic acid

A solution of 5.0 g of dl-4-hydroxy mandelic acid, 11.0 g of benzyl chloride and 10.0 g of potassium carbonate in 50 ml of methanol was heated to reflux and stirred for seventy-two hours. The reaction mixture was cooled to room temperature and diluted with 50 ml of water. The aqueous solution was washed twice with 50 ml portions of benzene, and then was acidified with concentrated hydrochloric acid. The aqueous acid solution was extracted three times with 50 ml portions of ethyl acetate. The organic extracts were combined, washed with water and with saturated sodium chloride solution and dried. Removal of the solvent by evaporation under reduced pressure provided 5.7 g of a solid which was then recrystallized from 300 ml of toluene to afford 5.33 g of dl-4-(benzyloxy)mandelic acid. M.P. 153°–155° C.

Analysis calc. for $C_{15}H_{14}O_4$:
Theory: C, 69.76; H, 5.46;
Found: C, 69.96; H, 5.33.

EXAMPLE 2

Resolution of dl-4-(benzyloxy)mandelic acid to R(−)-(4-benzyloxy)mandelic acid

To a stirred solution of 185.6 g of dl-4benzyloxy)mandelic acid in 2500 ml of ethyl acetate at 80° C. was added in one portion 43.6 g of R(+)-α-methylbenzylamine. The reaction mixture was cooled to room temperature, and the precipitated solid which had formed was collected by filtration and washed with fresh ethyl acetate. The solid was recrystallized twice from a solution of ninety percent ethanol in water to provide 91.4 g of the R(+)-α-methylbenzylamine salt of R(−)-4-(benzyloxy)mandelic acid. M.P. 208.5–209.5° C. $[\alpha]_D$ −38.6°, $[\alpha]_{365}$ −155.3° (MeOH)

Analysis calc. for $C_{23}H_{25}NO_4$:
Theory: C, 72.80; H, 6.64; N, 3.69;
Found: C, 72.95; H, 6.83; N, 3.95.

To a stirred suspension of 91.4 g of the above-named salt in 2000 ml of ethyl acetate was added 150 ml of ten percent aqueous hydrochloric acid solution. The aqueous acid solution was separated, and the organic layer washed with water and dried. Removal of the solvent by evaporation under reduced pressure afforded 54.5 g of R(−)-4-(benzyloxy)mandelic acid, i.e. R(−)-2-(4-benzyloxyphenyl)-2-hydroxyacetic acid. M.P. 155°–161° C. $[\alpha]_D$ −102.2°; $[\alpha]_{365}$ −410.6° (MeOH)

Analysis calc. for $C_{15}H_{14}O_4$:
Theory: C, 69.76; H, 5.46;
Found: C, 69.67; H, 5.41.

EXAMPLE 3

Preparation of dl-1-methyl-3-(4-benzyloxyphenyl)propylamine

A solution of 40.0 g of methyl 2-(4-benzyloxyphenyl-)ethyl ketone and 160 ml of anhydrous ammonia in 300 ml of ethanol was heated at 75° C. and stirred for two hours. After cooling the reaction mixture to room temperature, 4.0 g of Raney nickel was added in one portion, and the reaction mixture then was stirred at ° C. for twelve hours under a hydrogen atmosphere at 300 psi. The reaction mixture next was filtered and the filtrate was concentrated by evaporation of the solvent under reduced pressure to provide an oil. The oil was dissolved in 120 ml of 3N hydrochloric acid, from which the product as a hydrochloride salt precipitated. The salt so formed was collected by filtration and recrystallized from methanol and toluene to provide 36.2 g of dl-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride. M.P. 195°–197.5° C.

EXAMPLE 4

Resolution of dl-1-methyl-3-(4-benzyloxyphenyl)propylamine to provide R-(−)-1-methyl-3-(4-benzyloxyphenyl)propylamine

A solution of 629.3 g of dl-1-methyl-3-(4benzyloxyphenyl)propylaminium chloride was converted to the free amine by reaction with 95 g of sodium hydroxide in 400 ml of water. The free amine was then dissolved in 2000 ml of methylene chloride and added to a solution of 328 g of D-(−)-mandelic acid in 1000 ml of methanol. The mandelic acid salt of the free amine precipitated out of solution and was recrystallized three times from methanol to provide 322 g of the R-mandelic acid salt of R-1-methyl-3-(4-benzyloxyphenyl)propylamine. M.P. 166–167° C. $[\alpha]_D$ −30°, $[\alpha]_{365}$ −119° (MeOH).

The salt so formed was converted to R-1-methyl-3-(4-benzyloxyphenyl)propylamine as the free base by reaction with aqueous sodium hydroxide.

EXAMPLE 5

R,R-N-[2-(4-Benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine

A solution of 93.9 g of R-1-methyl-3-(4-benzyloxyphenyl)propylamine in 500 ml of N,N-dimethylformamide containing 63.0 g of 1-hydroxybenzotriazole and 104.6 g of R-2-(4-benzyloxyphenyl)-2-hydroxyacetic acid was cooled to 0° C. and stirred while a solution of 83.6 g of N,N'-dicyclohexylcarbodiimide in 300 ml of dimethylformamide was added dropwise over one hour. The reaction mixture was stirred for twelve hours at 3° C. and then was diluted with 10 ml of water, stirred for an additional hour, and then cooled to −30° C. in an ice-acetone bath. The reaction mixture was filtered to remove dicyclohexylurea, and then the filtrate was concentrated by evaporation of the solvent under reduced pressure. The concentrated solution was diluted with ethyl acetate and washed with saturated aqueous sodium carbonate solution, with water, with 300 ml of 1N hydrochloric acid, and again with water. The organic layer was dried and the solvent was removed by evaporation under reduced pressure to pro-

vide the product as a white solid. The solid was recrystallized once from acetonitrile and again from methanol to provide 159.7 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)-propylamine. M.P. 145°–148° C. $[\alpha]_D$ −15.9°, $[\alpha]_{365}$ −50.1° (MeOH).

Analysis calc for $C_{32}H_{33}NO_4$:
Theory: C, 77.55; H, 6.71; N, 2.83;
Found: C, 77.04; H, 6.84; N, 2.53.

EXAMPLE 6

R,R-N-[2-(4-Benzyloxyphenyl)-2-hydroxyethyl]-1-methyl3-(4-benzyloxyphenyl)propylamine

To a stirred solution of 10.0 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine in 500 ml of freshly distilled tetrahydrofuran under a nitrogen gas atmosphere was added dropwise over thirty minutes 41 ml of 2 molar borane-dimethyl sulfide complex in tetrahydrofuran. The reaction mixture was stirred at 25° C. for twenty hours, and then was heated to reflux and stirred for an additional three hours. After cooling the reaction mixture to 25° C. and stirring for another eighteen hours, the excess borane was decomposed by the slow portion-wise addition of 400 ml of methanol. The solvent was then removed from the reaction mixture by evaporation under reduced pressure to provide the product as an oil. The oil so formed was dissolved in 50 ml of hot methanol, and after concentrating the volume to 125 ml, the product began crystallizing out of solution. The crystalline product was collected by filtration and recrystallized twice from methanol to provide 6.65 g of R,R-N-[2-(4-benzyloxyphenyl)-2hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine. M.P. 119°–123.5° C.

The amine so formed was dissolved in methanol and added to a solution of ethereal hydrogen chloride, thereby providing 6.49 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride. M.P. 214.5°–216° C. $[\alpha]_D$ −13.4°, $[\alpha]_{365}$ −30.2° (MeOH).

Analysis calc. for $C_{32}H_{36}NO_3Cl$:
Theory: C, 74.19; H, 7.00; N, 2.70; Cl, 6.84;
Found: C, 74.20; H, 6.98; N, 2.65; Cl, 6.63.

EXAMPLE 7

R,R-1-(4-Hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride, also named as R,R-N[2-(4-Hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4hydroxyphenyl)propylaminium chloride

A mixture of 51.6 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride and 5.0 g of Raney nickel in 2 liters of ethanol and 2 liters of ethyl acetate was stirred at 25° C. for four and one-half hours under a hydrogen atmosphere of 60 psi. The reaction mixture was then filtered to remove the residual Raney nickel, and the filtrate was concentrated to an oil by evaporation of the solvent under reduced pressure, and the oil was crystallized from fresh ethanol and diethyl ether to provide 29.8 g of R,R-N-[2-(4-hydroxyphenyl)-2hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)-propylaminium chloride. M.P. 176°–176.5° C. (dec.) $[\alpha]_D$ −22.7°, $[\alpha]_{365}$ −71.2° (3.7 mg/ml MeOH).

Analysis calc. for $C_{18}H_{24}NO_3Cl$:
Theory: C, 63.99; H, 7.16; N, 4.15;
Found: C, 63.70; H, 7.26; N, 4.32.

EXAMPLE 8

As pointed out above, a preferred embodiment of this invention employs a mixture of all four optical isomers of the compound of Example 7. This racemic mixture can be prepared by the method described above by reaction of dl-4-(benzoyloxy)mandelic acid with dl1-methyl-3-(4-benzyloxyphenyl)propylamine in the presence of DCC to give racemic 1-(4-benzyloxyphenyl)-2-oxo-2-[1-methyl-3-(4-benzyloxyphenyl)propylamino]ethanol. Reduction of the latter compound and subsequent removal of the benzyl groups provides racemic 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol. This compound is more preferably prepared by the following procedure.

A solution of 32.8 g. (0.2 m) of methyl 2-(4-hydroxyphenyl)ethyl ketone and 42.6 g. (0.2 m) of 1-(4-hydroxyphenyl)-2-aminoethanol in 380 ml. of ethanol containing 3.8 g. of five percent palladium on carbon was stirred for sixteen hours at 60° C. under hydrogen at 55 psi. The reaction mixture was then filtered, and the filtrate was diluted by addition of 350 ml. of water. The aqueous mixture was concentrated to a volume of about 400 ml., and then washed with dichloromethane. The aqueous mixture was acidified by addition of 50 ml. of conc. hydrochloric acid. After standing at room temperature for two hours, the aqueous acid mixture was filtered and the filter cake was washed with 40 ml. of ice water and dried at 50° C. in vacuum to provide 47 g. of 1-(4-hydroxyphenyl-2[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride. M.P. 124°–129° C.

Analysis calc. for $C_{18}H_{24}NO_3Cl$:
Theory: C, 63.99; H, 7.16; N, 4.15; Cl, 10.49.
Found: C, 63.77; H, 6.80; N, 3.91; Cl, 10.68.

^{13}C NMR studies demonstrated the product to be comprised of 51% RR,SS diastereamer and 49% RS,SR diastereomer.

EXAMPLE 9

1-Phenyl-2-[1-methyl-3-(4-nitrophenyl)propylamino]ethanol

A solution of 5.0 g. (25.9 mM) of 2-amino-1-phenylethanol and 3.55 g. (25.9 mM) of methyl 2-(4-nitrophenyl)ethyl ketone in 60 ml. of toluene containing 10 mg. of para-toluenesulfonic acid was heated at reflux for six hours in a flask equipped with a Dean-Stark trap. The water that formed during the reaction was removed via the trap, and then the reaction mixture was cooled to room temperature and concentrated to dryness by evaporation of the solvent under reduced pressure. The solid product that remained was dissolved in 50 ml. of tetrahydrofuran and the solution was heated to reflux. A solution of 13.5 ml. of 2N borane-methyl sulfide complex in tetrahydrofuran was then added dropwise to the reaction mixture, and the mixture was refluxed for an additional ninety minutes. After cooling the reaction mixture to room temperature, it was diluted by addition of diethyl ether saturated with hydrogen chloride. The precipitate that formed was collected by filtration and crystallized from ethanol and diethyl ether to give 3.29 g. of 1-phenyl-2-[1-methyl-3-(4-nitrophenyl)propylamino]ethanol hydrochloride. M.P. 203–213° C.

Analysis calc. for $C_{18}H_{23}ClN_2O_3$:
Theory: C, 61.62; H, 6.61; N, 7.98; Cl, 10.11.
Found: C, 61.76; H, 6.62; N, 7.76; Cl, 10.13.

EXAMPLE 10

1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]ethanol

A solution of 32.6 g. (0.2 m) of 1,1- dimethyl-3-phenylpropylamine and 22.9 g. (0.1 m) of 2-(4-methoxyphenyl)-2-oxoethyl bromide in 75 ml. of tetrahydrofuran was heated at reflux for thirty-six hours. The reaction mixture was then cooled and added to 2 liters of diethyl ether. The precipitate was removed by filtration, and the filtrate was acidified with hydrobromic acid to give 18.15 g. of 1-(4- methoxyphenyl)-1-oxo-2-(1,1-dimethyl-3-phenylpropylamino)ethane hydrobromide. M.P. 174°–178° C.

The compound thus formed was dissolved in 85 ml. of glacial acetic acid containing 35 ml. of hydrobromic acid, and the solution was heated at reflux for nine hours. The solution was then cooled and the solvent was removed by evaporation to provide, following crystallization from ethanol and diethyl ether, 7.8 g. of 1-(4-hydroxyphenyl)-1-oxo-2-(1,1-dimethyl-3-phenylpropylamino)ethane hydrobromide. M.P. 228°–230° C.

Catalytic hydrogenation of 5.0 g. of the compound from above in 44 ml. of ethanol containing 1.25 g. of five percent palladium on carbon afforded, following crystallization from acetone and diethyl ether, 2.3 g. of 1-(4-hydroxyphenyl)-2-(1,1-dimethyl3-phenylpropylamino)ethanol hydrobromide. M.P. 168°–170° C.

Analysis calc. for $C_{19}H_{26}BrNO_2$:
Theory: C, 60.00; H, 6.89; N, 3.68.
Found: C, 60.28; H, 6.67; N, 3.62.

EXAMPLE 11

1-(3-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethanol

To a stirred solution of 67.2 g. (0.22 M) of 2-(3-benzyloxyphenyl)-2-oxoethyl bromide in 200 ml. of acetonitrile was added a solution of 54.3 g. (0.20 M) of N-benzyl-1,1-dimethyl-3-(4-fluorophenyl)propylamine in 600 ml. of acetonitrile containing 42 ml. (0.22 M) of diisopropylethylamine. The reaction mixture was stirred for about six hours at reflux, and then was cooled and stored at room temperature for forty-eight hours. The reaction mixture was next diluted by addition of aqueous sodium hydroxide, and the organic solvents were removed by evaporation under reduced pressure. The aqueous alkaline mixture was extracted with ethyl acetate, which was then washed with water, dried, and concentrated to dryness to give an oil. The oil was dissolved in ethanol and diethyl ether and converted to the hydrochloride salt by addition of excess hydrogen chloride. The precipitated solid was collected by filtration and recrystallized from ethyl acetate to give 51.3 g. of 1-(3-benzyloxyphenyl)-1-oxo-2-[(N-benzyl)-1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethane hydrochloride. M.P. 137°–145° C.

The compound thus prepared was reduced by reaction with 16 g. of sodium borohydride in ethanol. Isolation of the product, followed by conversion to the hydrochloride salt and crystallization from diethyl ether afforded 55.0 g. of 1-(3-benzyloxyphenyl)-2-[(N-benzyl)-1,1-dimethyl-3-(4-fluorophenyl)propylamino]-ethanol hydrochloride. M.P. 186.5°–191° C.

A solution of 10.0 g. of the product thus produced in 200 ml. of ethanol containing 3.0 g. of Raney Nickel was shaken for two hours at 25° C. under hydrogen at 44 psi. The reaction mixture was then filtered, and the solvent was removed from the filtrate by evaporation under reduced pressure to give a white solid. The solid was triturated with ethyl acetate and air dried to provide 5.9 g. of 1-(3-hydroxyphenyl)2-[1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethanol hydrochloride. M.P. 196.5°–198.5° C.

Analysis calc. for $C_{19}H_{25}ClFNO_2$:
Theory: C, 64.49; H, 7.12; N, 3.96; Cl, 10.02.
Found: C, 64.29; H, 6.97; N, 4.06; Cl, 9.89.

EXAMPLE 12

1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4aminocarbonylphenyl)propylamino]ethanol

A suspension of 10.0 g. (50 mM) of 1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamine and 15.0 g. (50 mM) of 1-(4-benzyloxyphenyl)-1-oxoethyl bromide in 1000 ml. of acetonitrile containing 32.0 g. (0.3 M) of sodium carbonate and 100 ml. of water was stirred for one hour at 25° C. The precipitate that formed was collected by filtration, washed with water and with diethyl ether, and air dried to provide 8.0 g. of 1-(4-benzyloxyphenyl)-1-oxo-2-[1,1-dimethyl-3(4-aminocarbonylphenyl)-propylamino]ethane. M.P. 184–187° C. This product was converted to the hydrochloride salt by reaction with hydrogen chloride in diethyl ether. M.P. 219°–224° C.

The compound thus prepared was reacted with sodium borohydride in methanol to provide, following conversion to the hydrochloride salt and crystallization from methanol and diethyl ether, 5.8 g. of 1-(4-benzyloxyphenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride. M.P. 141°–143° C.

Reaction of the above compound with hydrogen in the presence of Raney Nickel effected cleavage of the hydroxy protecting group to afford, following crystallization of the hydrochloride salt, 1.3 g. of 1-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride. M.P. 185°·C. (dec.)

Analysis calc. for $C_{20}H_{27}ClN_2O_3$:
Theory: C, 63.40; H, 7.18; N, 7.39; Cl, 9.36.
Found: C, 63.26; H, 7.01; N, 7.45; Cl, 9.42.

The compounds of Examples 13 and 14 were prepared by the general procedure of Example 12.

EXAMPLE 13

1-(2-Fluorophenyl)-2-[1,1-dimethyl-3-(4aminocarbonylphenyl)propylamino]ethanol hydrochloride

M.P. 227°–230° C.

EXAMPLE 14

1-(3-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl) propylamino]ethanol hydrobromide

M.P. 161°–165° C.

EXAMPLE 15

1-Phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl)-propylamino]ethanol hydrochloride

Methyl 2-(4-methylthiophenyl)ethyl ketone was oxidized by reaction with m-chloroperbenzoic acid to give methyl 2-(4-methylsulfonylphenyl)ethyl ketone. A solution of 6.73 g. of 2-amino-1-phenylethanol and 11.10 g. of methyl 2-(4-methylsulfonylphenyl)ethyl ketone in 500 ml. of toluene containing 200 mg. of p-toluenesulfonic acid was heated at reflux for twenty-four hours. The reaction mixture was cooled and the solvent was

removed by evaporation to give the Schiff base 1-phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl)-propylimino]ethanol. The Schiff base thus prepared was reacted with 3.7 g. of sodium borohydride in 500 ml. of ethanol at 0° C. for sixteen hours. The reaction mixture was diluted by addition of 50 ml. of acetone and 20 ml. of 3N hydrochloric acid. The mixture was concentrated to an oil by evaporation of the solvent. The oil crystallized upon standing at room temperature. Recrystallization of the product from 200 ml. of hot ethanol afforded 8.96 g. (48% yield) of 1-phenyl-2-[1-methyl-3-(4methylsulfonylphenyl)propylamino]ethanol hydrochloride. M.P. 164°–170° C.

Analysis calc. for $C_{19}H_{26}ClNO_3S$:

Theory: C, 59.44; H, 6.83; N, 3.65; Cl, 9.23; S, 8.35.

Found: C, 59.28; H, 6.57; N, 3.70; Cl, 9.36; S, 8.11.

EXAMPLE 16

Premix for Chickens

Ingredient	% by weight
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]-ethanol succinate	25
Ground Corn	74
Sodium Chloride	1
	100

EXAMPLE 17

Premix for ruminants

Ingredient	% by weight
1-(2-fluorophenyl)-2-[1,1-dimethyl-3-(4-aminocarbonyl-phenyl)propylamino]ethanol	30
Ground yellow corn	60
Alfalfa meal	10
	100

EXAMPLE 18

Premix for Swine

Ingredient	% by weight
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol hydrochloride	10
Soybean mill run	88
Mineral oil	2
	100

The above ingredients are blended to uniformity to provide a dry flowable premix that can be admixed with a typical animal feed ration at a rate to provide about 20 ppm of active ingredient in the final feed ration. For example, the premix can be added to the following swine grower ration for convenient oral administration of the β-phenethanolamine to swine.

Ingredient	% by weight	lbs/Ton
Corn, yellow, ground	76.70	1534
Soybean Oil Meal, solvent extracted, dehulled	19.35	387
Calcium Carbonate	1.20	24
Dicalcium Phosphate, feed grade	1.20	24
Salt (sodium chloride)	0.50	10
Trace mineral premix, AN-03[1]	0.10	2
Swine Vitamin Premix, SW-03[2]	0.65	13
Vitamin A Premix, 3M USP units/lb.[3]	0.05	1
Methionine Hydroxy Analogue, 93%	0.20	4
Selenium Premix[4]	0.005	1
	100.00	2000

[1]Each Kg of premix contains: 50 g. manganese as manganese sulfate; 100 g. zinc as zinc carbonate; 50 g. iron as ferrous sulfate; 5 g. copper as copper oxide; 1.5 g. iodine as potassium iodide and 150 g. maximum and 130 g. minimum calcium as calcium carbonate.

[2]Each Kg of premix contains: 77,161 IU Vitamin D_3; 2,205 IU Vitamin E; 411 mg. riboflavin; 1,620 mg. pantothenic acid; 2,205 mg. niacin; 4.4 mg. Vitamin B_{12}; 441 mg. Vitamin K; 19,180 mg. choline; 110 mg. folic acid; 165 mg. pyridoxine; 110 mg. thiamine; 22 mg. biotin.

[3]Each Kg of premix contains 6,613,800 IU Vitamin A.

[4]Each Kg of premix contains 200 mg. of selenium as sodium selenite.

EXAMPLE 19

Feed Ration for Lambs

Ingredient	Percent	lbs/T
Yellow corn	61.00	1220.0
Corn cobs	20.00	400.0
Alfalfa Meal, dehydrated	5.40	108.0
Soybean oil meal	8.00	160.0
Urea, feed grade	0.50	10.0
Molasses, cane	3.00	60.0
Dicalcium phosphate	0.43	8.6
Salt	0.30	6.0
Calcium carbonate	0.14	2.3
Trace mineral premix[1]	0.03	0.6
Vitamin A + D_3 Premix[2]	0.10	2.0
Vitamin E Premix[3]	0.10	2.0
1-(4-Hydroxyphenyl)-2-(1,1-dimethyl-3-phenylpropylamino)-ethanol	1.00	20.0
	100.00	2000.0

[1]Trace mineral premix contains: 2.5% manganese as manganese oxide, 0.07% iodine as potassium iodide, 0.3% cobalt as cobalt carbonate, 0.5% copper as copper oxide, and 20.0% zinc as zinc sulfate.

[2]Each pound of vitamin A and D_3 premix contains 2,000,000 USP units Vitamin A and 225,750 USP units Vitamin D_3.

[3]Each pound of Vitamin E premix contains 20,000 IU Vitamin E.

The compounds to be employed in the method of this invention have demonstrated efficacy in animal tests designed to establish beneficial nutritional effects. In one test designed to show lipolytic activity, normal swine, either barrows or gilts, were employed to analyze the effect of compounds on blood glucose, insulin, and non-esterified fatty acids (NEFA).

Test animals were maintained in metabolism crates, and following a period of adaptation, catheters were placed in their femoral veins. Prior to administration of the test compounds, all animals were fasted for a period of forty hours. Such fasting causes an elevation of NEFA's in the blood. On the day of the test, all animals were fed a normal feed ration, and one group of animals were held as controls while another group of animals received a test compound. The test compounds were administered at 200 mcg/kg intravenously, or orally at 1 mg/kg. Blood samples were taken from each animal immediately prior to treatment and then at one hour intervals for a period of six hours following treatment. The blood plasma was analyzed for glucose, insulin and NEFA content.

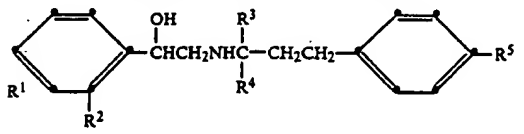
When the fasted pigs were fed the normal feed ration without a test compound, the NEFA levels in the blood

drop dramatically and remained low. A β-phenethanolamine as defined herein caused either an elevation in NEFA's, or inhibited the drop in NEFA's. Blood levels of glucose and insulin were also elevated with the β-phenethanolamines.

The following Table presents the lipolytic activity of several preferred β-phenethanolamines when evaluated according to the test described above. The results are averages of several tests.

TABLE I

Lipolytic Activity (increase in NEFA's)



R^1	R^2	R^3	R^4	R^5	% increase in NEFA's over control	% increase in glucose over control
H	H	H	CH_3	SO_2CH_3	131	9
p-OH	H	CH_3	CH_3	H	445	48
m-OH	H	CH_3	CH_3	H	71	31
m-OH	H	CH_3	CH_3	F	28	72
p-OH	H	CH_3	CH_3	OH	141	35
p-OH	H	CH_3	CH_3	$CONH_2$	18	169
m-OH	H	CH_3	CH_3	OH	68	40
H	H	H	H	NO_2	199	7
p-OCH_3	H	CH_3	CH_3	H	84	25
p-OCH_3	H	CH_3	CH_3	OH	249	5
H	H	H	CH_3	NO_2	1458	27

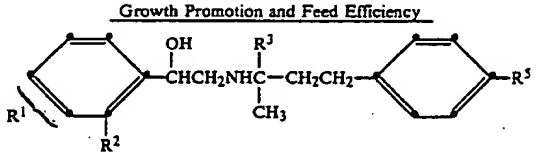
A ten day in vivo study was employed to determine the effect of β-phenethanolamines on feed efficiency and rate of growth. In these studies, barrows and gilts weighing approximately 60 kg were maintained in individual pens. Each treatment was replicated six times in randomly assigned animals, with each test animal forming an experimental unit. A group of control animals received a normal swine grower feed ration comprising the following ingredients:

Ingredient	% by weight
Ground yellow corn	76.70
Soybean oil meal	19.35
Calcium carbonate	1.20
Dicalcium phosphate	1.20
Salt	0.50
Trace mineral premix	0.10
Swine Vitamin premix	0.65
Vitamin A premix, 3M USP units/lb.	0.05
Methionine Hydroxy analogue, 93%	0.20
Selenium premix	0.05
	100.00

The test animals received the same feed ration plus the test compound. All animals received feed and water ad libitum. All animals were weighed on day 1 and again on day 10, and feed consumption was measured by recording all feed issued and any remaining feed on day 10. The results of two series of this 10 day test for several β-phenethanolamines are given in Table II. In the Table, the column labelled "ADG" is the average daily weight gain in pounds; "ADF" is the average daily feed consumption (in pounds) by the test animals; and F/G is the feed efficiency calculated as ADF divided by ADG.

TABLE II

Growth Promotion and Feed Efficiency



R^1	R^2	R^3	R^5	dose ppm	ADG	ADF	F/G
Experiment I							
Control					1.60	4.7	2.98
p-OH	H	H	OH	20	2.19	5.0	2.33
H	H	H	NO_2	20	1.78	4.22	2.37
Experiment II							
Control					1.34	4.16	3.22
p-OH	H	CH_3	H	20	1.60	4.26	2.66
m-OH	H	CH_3	F	20	1.52	4.57	3.01

The β-phenethanolamines to be employed in the method of this invention can be administered in combination with other compounds known to have a beneficial effect upon animals. Typical compounds to be coadministered with the β-phenethanolamines include antibiotics, for example any of the tetracyclines, tylosin, penicillins, cephalosporins, polyether antibiotics, glycopeptides, orthosomycins and related compounds commonly administered to swine, poultry, ruminants and the like. A preferred combination to be employed in the present method is an antibiotic such as tylosin or a tetracycline, together with 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol. Such combinations will comprise the respective components in a ratio of about 1 to about 2 parts by weight of β-phenethanolamine and about 1 to about 10 parts by weight of the partner component.

In a typical treatment, 1-(4-hydroxyphenyl)2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol was evaluated in a 42-day study employing finishing swine. Each treatment was replicated four times, with three pigs per replication. All treatments included a normal feed diet plus tylosin at 40 g/T. The animals were tested for growth performance and feed efficiency enhancement. Carcass quality was determined by analysis for fat and muscling. The results of the study are given in Table III. Both β-phenethanolamine treatments resulted in improved growth performance and carcasses with less fat and more muscle.

TABLE III

Growth Promotion, Feed Efficiency and Carcass Quality

	β-phenethanolamine[2]				
	Control[1]	20 g/T	% change	40 g/T	% change
ADG	1.94	2.07	(6.7)	2.05	(5.7)
ADF	6.28	6.63	(5.6)	6.64	(5.7)
F/G	3.24	3.20	(−1.2)	3.24	(0)
Live Wt. at Slaughter, lb	217.0	223.0	(2.8)	221.0	(1.8)
Chilled Carcass Wt., lb	154.6	160.5	(3.8)	159.8	(3.4)

TABLE III-continued

Growth Promotion, Feed Efficiency and Carcass Quality	β-phenethanolamine[2]				
	Control[1]	20 g/T	% change	40 g/T	% change
Fat Depth at 10th Rib, in	1.15	1.09	(−5.2)	1.05	(−8.7)
Loin Eye Area Sp., in	4.64	4.91	(5.8)	4.84	(4.3)
Estimated pounds of Fat Free Muscle[3]	74.2	78.8	(6.1)	78.4	(5.7)

[1]all diets contained 40 g/T of tylosin
[2]1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol hydrochloride
[3]A regression equation was employed in arriving at the numerical predictions of carcass muscle (J. Animal Science, 1977, Vol. 44:8–17).

The data reported in Table III further demonstrates that the β-phenethanolamines described herein promote growth, improve feed efficiency and improve leaness.

In a similar study conducted over a 61 day period, a group of control animals received a normal daily feed ration with no additive. Another group of animals received the feed ration plus tylosin at 40 g/T, while another group received the feed ration plus 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride (compound A) at 20 g/T. A final group of finishing swine received the feed ration plus the combination of 40 g/T of tylosin and 20 g/T of the phenethanolamine. The results of this trial are given in Table IV.

TABLE IV

	Control	Tylosin	A	Tylosin + A
ADG	1.63	1.64	1.36	1.50
ADF	5.64	5.77	5.10	5.38
F/G	3.46	3.51	3.77	3.59
Slaughter Wt, (lbs)	210	211	193	201
Carcass Wt, (lbs)	150.3	151.5	140.1	146.3
Fat Depth, 10th rib, (in)[1]	0.96	0.96	0.80	0.85
Loin Eye Area (in^2)[1]	4.60	4.68	4.92	5.00
Est. % Muscle[2]	49.2	49.2	51.4	51.2
Est. Pounds Muscle[2]	75.3	76.5	74.1	76.8

[1]These results are based upon measurement of fat at the 10th rib after the carcass is split in half across the backbone.
[2]A regression equation is employed in arriving at the numerical predictions of carcass muscle (J. Animal Science, 1977, Vol. 44:8–17).

As in the previous study, both phenethanolamine treatments resulted in carcasses with less fat and more muscle. It should also be noted that the estimated amount of carcass muscle produced with the Tylosin +A treatment was similar to that produced in the control and the Tylosin treatment alone. This result was achieved, however, with less feed consumption than either the control or the Tylosin treatments.

Additional studies have been carried out to demonstrate the anabolic effect of β-phenethanolamines in swine. The effect of the compounds on nitrogen retention in finishing barrows was determined. Nitrogen retention is the difference between nitrogen intake and nitrogen excreted. Increased nitrogen retention is known to be associated with increased anabolic activity, resulting in improved carcass muscling and leanness.

In a typical study, barrows weighing about 172 pounds (78 Kg) were orally administered various doses of 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride (Compound A). All animals received water and a constant amount of normal swine feed ration. The results of this study are presented in Table V, and show that all β-phenethanolamine treatments improved nitrogen retention compared to controls.

TABLE V

	Nitrogen Retention	
Treatment	Animals per treatment	Nitrogen Retained (g/day)
Control	6	21.0
Compound A (5 g/T)	3	23.6
Compound A (10 g/T)	3	23.9
Compound A (20 g/T)	3	25.0

As pointed out above, the method of this invention can be practiced with individual isomers of β-phenethanolamines or with mixtures of isomers and diastereomers. In a study to determine the effect on weight gain and feed efficacy of various mixtures of diastereomers, barrows initially weighing about 177 pounds were fed a normal swine diet plus a β-phenethanolamine at 20 g/T of feedstuff. Each treatment was replicated in twelve individually fed animals. The results are presented in Table VI and show that growth performance was improved by both β-phenethanolamine treatments with very little change in feed intake.

TABLE VI

Treatment	Average Daily Feed (lbs)	Average Daily Gain (lbs)
Control	5.89	1.58
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride 57.5% RR,SS 42.5% RS,SR	5.94	2.15
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride 47% RR,SS 53% RS,SR	5.86	1.95

The data in Table VI demonstrates that the method of improving feed efficency and promoting growth can be practiced with any desired mixture of β-phenethanolamine optical isomers.

The efficacy of the β-phenethanolamines described herein also has been demonstrated in poultry. In a typical study, broilers that were twenty-one days old were administered an oral dosing of a β-phenethanolamine in their normal daily feed ration. All animals received the following broiler finisher ration;

Ingredients	% by weight	lbs/T
Ground yellow corn	66.40	1328.00
Animal-vegetable fat	1.53	30.60
Corn Glut. meal (60%)	4.00	80.00
Soybean meal (48%)	19.19	383.80

-continued

Ingredients	% by weight	lbs/T
Fish meal-menhaden	2.50	50.00
Dicalcium phosphate	1.01	34.20
Feather meal-Hydr.	2.50	50.00
Ground limestone	0.83	16.60
Salt	0.30	6.00
Vitamin Premix[1]	0.50	10.00
Trace mineral premix[2]	0.10	2.00
Methionine Hyd. Anal.	0.15	3.00
Lysine HCl	0.29	5.80
	100.00	2000.00

[1]Vitamin premix provides 3000 IU of vitamin A, 900 ICU of vitamin D_3, 40 mg. of vitamin E, 0.7 mg. of vitamin K, 1000 mg of choline, 70 mg. of niacin, 4 mg of pantothenic acid, 4 mg of riboflavin, 100 mcg of vitamin B_{12}, 100 mcg of biotin and 125 mg of ethoxyquin per kg of complete feed.

[2]Trace mineral premix provides 75 mg of manganese, 50 mg of zinc, 25 mg of iron and 1 mg of iodine per kg of complete feed.

Test animals received with the above ration varying doses of 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride (compound A). Each treatment was replicated sixteen times, and the test was terminated when the animals reached fifty-six days of age. The animals were analyzed for weight gain and feed efficiency. The results of this test in broilers is presented in Table VII as mean weight gain and mean feed to gain ratios.

TABLE VII

		Growth Performance of Broilers			
		Weight Gain		Feed Efficiency	
Treatment	Dose (g/T)	grams	% improvement	Feed/Gain Ratio	% change from control
Control		1473	0	2.336	0
Compound A	10	1585	7.6	2.292	1.9
Compound A	20	1613	9.5	2.298	1.6
Compound A	40	1550	5.2	2.312	1.0
Compound A	80	1669	13.3	2.221	4.9

The results of this study demonstrate that the β-phenethanolamines described herein are effective in promoting growth and improving feed efficiency in poultry.

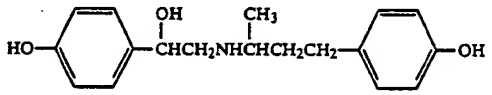
The compounds of the invention also have demonstrated efficacy in ruminants. Forty-eight crossbred wether lambs were employed in a test designed to show the effects of Compound A (1-(4-hydroxyphenyl)2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride) at varying doses. Sixteen animals were held as controls, while sixteen received 40 ppm of Compound A, and another sixteen received 80 ppm of Compound A. All animals received a normal daily feed ration and water ad libitum. Average daily weight gain and average daily feed consumption after twenty-eight days is given below in Table VIII. The data demonstrates that a β-phenethanolamine as defined herein is effective in promoting growth and improving feed efficiency in ruminants.

TABLE VIII

	Growth Performance of Lambs			
Treatment	Dose (ppm)	ADG (lbs)	ADF (lbs)	F/G
Control	0	0.414	3.68	8.89
Compound A	40	0.418	3.61	8.64
Compound A	80	0.472	3.57	7.56

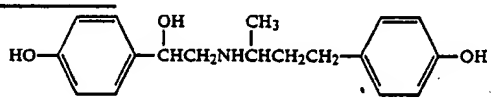
We claim:

1. A method for promoting the growth of swine comprising administering to the animal a growth promoting amount of a compound having the formula



or an acid addition salt thereof.

2. A method for improving the efficiency of feed utilization by swine comprising administering to swine an effective amount of a compound of the formula



or an acid addition salt thereof.

3. The method of claim 1 employing R,R-N-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)propylamine, or an acid addition salt thereof.

4. The method of claim 2 employing R,R-N-2-(4-hydroxyphenyl)-2-hydroxyethyl]-1-methyl-R,R-N-[-(4-hydroxyphenyl)propylamine, or an acid addition salt thereof.

5. The method of claim 1 employing N-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)propylamine hydrochloride.

6. The method of claim 2 employing N-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)propylamine hydrochloride.

7. The method of claim 3 employing R,R-N-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)propylamine hydrochloride.

8. The method of claim 4 employing R,R-N-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)propylamine hydrochloride.

* * * * *

Exhibit XII

U.S. Patent 4,849,453

United States Patent [19]

Anderson et al.

[11] **Patent Number: 4,849,453**

[45] **Date of Patent: Jul. 18, 1989**

[54] **GROWTH PROMOTION**

[75] Inventors: **David B. Anderson**, Greenfield; **Klaus K. Schmiegel**, Indianapolis; **Edward L. Veenhuizen**, Greenfield, all of Ind.; **Ronald R. Tuttle**, Escondido, Calif.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[21] Appl. No.: **153,640**

[22] Filed: **Feb. 8, 1988**

Related U.S. Application Data

[60] Division of Ser. No. 860,719, May 7, 1986, Pat. No. 4,734,437, which is a continuation of Ser. No. 628,002, Jul. 5, 1984, abandoned, which is a continuation of Ser. No. 462,587, Jan. 31, 1983, abandoned.

[51] **Int. Cl.**[4] **A61K 31/135**

[52] **U.S. Cl.** **514/653**

[58] **Field of Search** 514/653

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,818,101	6/1974	Baile et al.	424/300
3,966,814	6/1976	Schromm et al.	260/570.6
4,086,272	4/1978	Cox et al.	260/559 D
4,279,925	7/1981	Haynes	424/311
4,305,960	12/1981	Haynes	424/330
4,338,333	7/1982	Ainsworth et al.	424/309
4,391,826	7/1983	Mills et al.	424/324

FOREIGN PATENT DOCUMENTS

6735	1/1980	European Pat. Off. .	
7206	1/1980	European Pat. Off. .	
26298	4/1981	European Pat. Off. .	
49728	4/1982	European Pat. Off. .	
793295	2/1981	South Africa .	
793296	2/1981	South Africa .	
2028801	3/1980	United Kingdom	514/653

OTHER PUBLICATIONS

Fed. Proc., 42, #4 (1983); 42, #3 (1983).

J. Pharm. Pharmacol., 18(3), 188–189 (1966), "The Effects of Some Derivatives of Noradrenaline and 2-amino-1-p-hydroxy-phenylethanol on the In Vitro Mobilisation of Fat".

Rec. trav. chim., 74, 919–936 (1955), "Synthesis of B—Phenyl-Ethylamine Derivatives. III) Bronchodilators", H. D. Moed et al.

Rec. trav. chim., 71, 933–944 (1952) ("Synthesis of B—Phenyl-Ethylamine Derivatives. II), Condensation of Phenols with Amino-Acetonitriles", H. D. Moed et al.

Chemical Abstracts, 47:2360g.

Chemical Abstracts, 54:25264b.

Chemical Abstracts, 62:10372d.

Chemical Abstracts, 45:1252g.

Chemical Abstracts, 46:11427h.

Chemical Abstracts, 49:1793i.

Chemical Abstracts, 65:15942.

Baker et al., Use of an Adrenergic Agonist to Alter Muscle and Fat Deposition in Lambs, *Fed. Prod.*, 42, 1983 (3069).

Ricks et al., Use of a β-Agonist to Alter Fat and Muscle Deposition in Steers, *Fed. Proc.*, 42, 1983 (3070).

Dalrymple et al., Use of the β-Agonist Clenbuterol to Alter Carcass Composition in Poultry, *Fed. Proc.*, 42, 1983 (2203).

Borsini et al., *Life Sciences*, 30, pp. 905–911 (1982).

Van Dijk et al., Recueil, 92, 1281–1297 (1973).

Primary Examiner—Frederick E. Waddell

Attorney, Agent, or Firm—Donald R. Stuart; Leroy Whitaker; C. W. Ashbrook

[57] **ABSTRACT**

β-Phenethanolamines are effective in promoting growth and improving feed efficiency and leanness in animals.

2 Claims, No Drawings

GROWTH PROMOTION

this application is a division of application Ser. No. 860,719, filed 5/7/86, now U.S. Pat. No. 4,734,437, which is a continuation of Ser. No. 628,002, filed 7/5/84, now abandoned, which is a continuation of Ser. No. 462,587, filed 1/31/83, now abandoned.

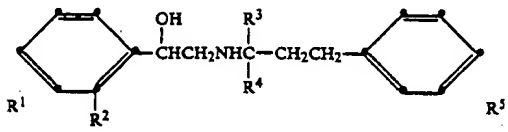
BACKGROUND OF THE INVENTION

The chemistry and use of β-phenethanolamines has been extensively investigated. A number of these compounds have been reported to have beneficial cardiac activities; see U.S. Pat. No. 3,987,200. Such compounds also are known to have sympathomimetic activity, and have found utility as utero-relaxing agents; Van Dijk et al., *Recueil*, 92, 1281 (1973). More recently, a group of β-hyperglycemic activity, and have been found effective in promoting the loss of weight in animals, EPO 6735 published Jan. 9, 1980.

An object of this invention is to provide a new use for certain β-phenethanolamines. This invention provides a method for promoting the growth of domesticated animals employing β-phenethanolamines.

SUMMARY OF THE INVENTION

This invention provides a method for increasing weight gain in animals and improving the efficiency of feed utilization and the quality and the quallty of the carcass. The invention is more particularly directed to a method for promoting growth and improving feed efficiency and leanness comprising administering an effective amount of a compound having the formula



wherein:

R^1 is hydrogen, hydroxy, or methoxy;

R^2 is hydrogen or fluoro,

R^3 is hydrogen or C_1–C_2 alkyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, fluoro, nitro, hydroxy, SO_2CH_3 or $CONH_2$; provided that R^1 is hydrogen only when R^5 is nitro or SO_2CH_3; and the acid addition salts thereof.

A preferred method for promoting growth and improving feed efficency and leanness according to this invention employs a compound of the above formula wherein R^1 is hydroxy, R^2 is hydrogen, R^3 is hydrogen or methyl and R^4 is methyl. The method is most preferably practiced employing a compound wherein R^1 and R^5 both are hydroxy and R^2 and R^3 both are hydrogen and R^4 is methyl. When R^1 is hydroxy or methoxy, it preferably is in the para position. When R^5 is other than hydrogen, it also is preferably in the para position.

This invention also provides an animal feed-stuff comprising a β-phenethanolamine of the above formula together with a suitable carrier therefor.

DETAILED DESCRIPTION OF THE INVENTION

The compounds employed in the method provided by this invention are either known in the art or are readily prepared by well known synthetic procedures. A particularly preferred method employs 1-(3-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]-ethanol. This β-phenethanolamine is disclosed in South African Pat. No. 673,994 published in May, 1967. The most preferred embodiment of this invention employs 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol, a compound disclosed as having utero-relaxing activity by Van Dijk et al. in *Recueil*, 92 1281 (1973).

The compounds to be employed in the method of this invention are readily prepared by reaction of a styrene oxide with a 3-phenylpropylamine derivative. For example, a styrene oxide such as 2-fluorostyrene oxide can be reacted with about an equimolar quantity of an amine such as 1-methyl-3-(4-nitrophenyl)propylamine in an unreactive organic solvent such as ethanol, methanol, n-propanol, dioxane, or the like. The reaction generally is carried out at a temperature of about 50° to about 120° C., and at such temperature the reaction routinely is substantially complete within about 6 to about 10 hours. The product, a β-phenethanolamine, is readily isolated by simply removing the reaction solvent, for instance by evaporation under reduced pressure, and further purification can be accomplished if desired by standard techniques, including crystallization, chromatography, acid-base extraction, and the like.

An alternative method for preparing the β-phenethanolamines to be employed in the present method comprises reacting a mandelic acid derivatives with a 3-phenylpropylamine derivative to provide an amide, which upon subsequent reduction provides a compound of the above formula. For example, a phenylpropylamine derivative such as 1-methyl-3-(3-fluorophenyl)-propylamine can be reacted with an acrylating agent such as a hydroxy protected mandelic acid halide, or preferably simply reacted with a mandelic acid in the presence of a common peptide coupling reagent such as N,N'-dicyclohexylcarbodiimide, carbonyldiimidazole, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, commonly referred to as EEDQ. The direct coupling reaction generally is conducted in an organic solvent such as benzene or N,N-dimethylformamide, and normally is complete after about 2 to 48 hours when carried out at about −30° to about 100° C. The product is an amide that is readily isolated by simply filtering the reaction mixture and then removing the reaction solvent. The amide thus formed is next reduced by reaction with a common reducing agent such as diborane or the like to provide a β-phenethanolamine defined by the above formula.

A similar, yet alternative, method of synthesis comprises reacting a phenethanolamine with a phenylethyl ketone to provide a Schiff base, which upon reduction gives a compound to be employed in the present method. For example, a phenethanolamine such as 2-hydroxy-2-(4-hydroxyphenyl)ethylamine can be reacted with a ketone such as methyl 2-(4-hydroxyphenyl)ethyl ketone to provide the corresponding imine, which upon reduction, for instance with 5% palladium on carbon, provides 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol.

It should be noted that the compounds to be employed in the method of this invention possess at least one asymmetric center (i.e. the carbinol center), and when R^3 and R^4 differ, the compounds possess two asymmetric centers. Since employment of individual optical isomers necessitates preparing the β-phene-

thanolamines from optically active starting materials, or using costly separation procedures, a preferred embodiment of this invention employs a mixture of optical isomers. For example, 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol is preferably prepared from racemic mixtures of starting materials, e.g. dl-1-methyl-3-(4-hydroxyphenyl)propylamine and dl-4-hydroxystyrene oxide, to provide a mixture of all four possible optical isomers of the product. The mixture of optical isomers is employed in the method without subsequent separation of isomers.

Since the β-phenethanolamines to be employed in the present method are inherently basic, they readily form acid addition salts with any number of inorganic and organic acids. These salts can be employed in the method of the invention, and often are preferred to the free base since they generally are more soluble in solvents such as water and are more conveniently formulated as an animal feedstuff. Acids commonly employed to form acid addition salts include mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid, perchloric acid and the like; and organic acids such as acetic acid, citric acid, succinic acid, para-toluene sulfonic acid, methanesulfonic acid, lactic acid and the like. Preferred salts to be employed in the present method include the hydrochlorides and hydrobromides.

Typical β-phenethanolamines to be employed in the method of this invention include the following:

1-(3-hydroxyphenyl)-2-[1-methyl-1-ethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol;
1-(2-fluoro-4-hydroxyphenyl)-2-[1-methyl-3-(4-fluorophenyl)propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[3-(3-nitrophenyl)-propylamino]ethanol;
1-(3-hydroxy-2-fluorophenyl)-2-[3-(4-methylsulfonyl)propylamino]ethanol;
1-(4-methoxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol;
1-phenyl-2-[1,1-dimethyl-3-(3-methylsulfonyl-phenyl)propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride;
1-(phenyl)-2-[1-methyl-3-(4-nitrophenyl)-propylamino]ethanol;
1-(3-hydroxyphenyl)-2-[1-methyl-3-(4-fluorophenyl)-propylamino]ethanol succinate;
1-(4-hydroxyphenyl)-2-[1-methyl-1-ethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-phenyl-propylamino]ethanol hydrobromide; and
d-1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol.

The method of promoting growth and improving leanness and feed efficiency provided by this invention is practiced by administering an effective amount of a compound defined above to a warm-blooded animal that receives a nutritionally adequate diet. The method generally will be practiced on domesticated animals raised for human meat consumption, for example grower/finisher swine, poultry, ruminants and the like. In a preferred embodiment, the growth of pigs, chickens and turkeys is promoted employing a β-phenethanolamine. Another preferred embodiment is practiced in ruminants such as cattle, sheep and goats. The method of improving leanness is not limited to meat producing animals, and can be practiced on other warm-blooded animals, including dogs and cats. This latter embodiment is particularly useful when it is desired to maintain mature animals in a relatively lean physical state.

The method of the invention is preferably practiced by orally administering an effective amount of a β-phenethanolamine to an animal. Other routes of administration can be employed, for instance intramuscular or intravenious injection; however, such routes are less practical. The amount to be administered to an animal is an amount that is effective in causing a promotion of growth, or an improvement in the efficiency of utilization of food, or an improvement in carcass quality of the animal, for instance in the form of less fatty tissue and improved leanness. The effective amount to be administered will vary somewhat depending upon the particular animal species being treated and the particular active ingredient employed, but generally will be from about 1 to about 1000 parts per million (ppm) of total daily feed intake. Such amount will provide a dosage of about 0.05 to about 50 mg/kg. A preferred embodiment employs about 1 to about 200 ppm, and more preferably from about 5 to about 1000 ppm. A typical amount of active ingredient to be administered to swine will be from about 5 to about 40 ppm. For example, when practicing the method in animals such as ruminants or swine, the compound will be added to the daily feed ration at about 5 to about 100 parts per million of the daily feed ration.

For oral administration, the active β-phenethanolamine is preferably admixed with suitable carriers or diluents commonly employed in animal husbandry. Animal feedstuffs comprising a β-phenethanolamine growth promoter as defined herein are provided as a further embodiment of this invention. Typical carriers and diluents commonly employed in such feedstuffs include corn meal, soybean meal, alfalfa meal, rice hulls, soybean mill run, cottonseed oil meal, bone meal, ground corn, corncob meal, sodium chloride, urea, cane molasses and the like. Such carriers promote a uniform distribution of the active ingredient in the finished feed ratio into which such compositions are added, thereby ensuring proper distribution of the active ingredient throughout the feed. The feedstuff composition provided by the invention will contain about 5 to about 95 percent by weight of active ingredient, and more typically about 10 to about 50 percent by weight. As already noted, the acid addition salts of the active phenethanolamines are generally preferred for oral administration, and are thus the preferred form of active ingredient for the feedstuff compositions of the invention.

While the preferred method for orally administering the growth promoters is via the daily feed rations, the compounds can be incorporated into salt blocks and mineral licks, as well as being added directly to drinking water for convenient oral consumption. The compounds can additionally be formulated with polymorphous materials, waxes and the like for long-term controlled release, and administered to an animal as a bolus or tablet only as needed to maintain the desired daily payout of active ingredient.

For parenteral administration, the β-phenethanolamines can be admixed with conventional carriers such as corn oil, sesame oil, carbowax, calcium stearate and the like. Such formulations can be molded into pellets and administered as an injection or as a slow-release subcutaneous implant. Such administrations can be made as often as needed to ensure the proper dosing of active ingredient to obtain the desired rate of growth

promotion and improvement in leanness and feed efficiency.

While the compounds described herein are effective in promoting average daily weight gain and improving feed efficiency in animals, they also cause observable improvement in the quality of the meat produced. For example, the compounds appear to mobilize free fatty acids from fatty tissue and depress the deposition of fat as the animals gain weight. This reduction of fat is beneficial since the animal being treated according to the invention gains weight in the form of more useable lean meat, thereby reducing waste and improving the value of the animal thus treated. Also, mature animals that are not subject to additional weight gain can be maintained in a desirably lean form by administering a compound as described herein.

The practice of the present invention is more fully illustrated by the following detailed examples.

EXAMPLE 1

Preparation of dl-4-(benzyloxy)mandelic acid

A solution of 5.0 g of dl-4-hydroxy mandelic acid, 11.0 g of benzyl chloride and 10.0 g of potassium carbonate in 50 ml of methanol was heated to reflux and stirred for seventy-two hours. The reaction mixture was cooled to room temperature and diluted with 50 ml of water. The aqueous solution was washed twice with 50 ml portions of benzene, and then was acidified with concentrated hydrochloric acid. The aqueous acid solution was extracted three times with 50 ml portions of ethyl acetate. The organic extracts were combined, washed with water and with saturated sodium chloride solution and dried. Removal of the solvent by evaporation under reduced pressure provided 5.7 g of a solid which was then recrystallized from 300 ml of toluene to afford 5.33 g of dl-4-(benzyloxy)mandelic acid. M.P. 153°–155° C.

Analysis calc. for $C_{15}H_{14}O_4$.
Theory: C, 69.76; H, 5.46.
Found: C, 69.96; H, 5.33.

EXAMPLE 2

Resolution of dl-4-(benzyloxy)mandelic acid to provide R(−)-(4-benzyloxy)mandelic acid

To a stirred solution of 185.6 g of dl-4-benzyloxy)-mandelic acid in 2500 ml of ethyl acetate at 80° C. was added in one portion 43.6 g of R(+)-α-methylbenzylamine. The reaction mixture was cooled to room temperature, and the precipitated solid which had formed was collected by filtration and washed with fresh ethyl acetate. The solid was recrystallized twice from a solution of ninety percent ethanol in water to provide 91.4 g of the R(+)-α-methylbenzylamine salt of R(−)-4-(benzyloxy)mandelic acid. M.P. 208.5°–209.5° C. $[\alpha]_D$ −38.6°, $[\alpha]_{365}$ −155.3° (MeOH).

Analysis calc. for $C_{23}H_{25}NO_4$.
Theory: C, 72.80; H, 6.64; N, 3.69.
Found: C, 72.95; H, 6.83; N, 3.95.

To a stirred suspension of 91.4 g of the above-named salt in 2000 ml of ethyl acetate was added 150 ml of ten percent aqueous hydrochloric acid solution. The aqueous acid solution was separated, and the organic layer washed with water and dried. Removal of the solvent by evaporation under reduced pressure afforded 54.5 g of R(−)-4-(benzyloxy)mandelic acid, ie. R(−)-2-(4-benzyloxyphenyl)-2-hydroxyacetic acid. M.P. 155°–161° C. $[\alpha]_D$ −102.2°; $[\alpha]_{365}$ −410.6° (MeOH).

Analysis calc. for $C_{15}H_{14}O_4$.
Theory: C, 69.76; H, 5.46.
Found: C, 69.67; H, 5.41.

EXAMPLE 3

Preparation of dl-1-methyl-3-(4-benzyloxyphenyl)propylamine

A solution of 40.0 g of methyl 2-(4-benzyloxyphenyl-)ethyl ketone and 160 ml of anhydrous ammonia in 300 ml of ethanol was heated at 75° C. and stirred for two hours. After cooling the reaction mixture to room temperature, 4.0 g of Raney nickel was added in one portion, and the reaction mixture then was stirred at 25° C. for twelve hours under a hydrogen atomsphere at 300 psi. The reaction mixture next was filtered and the filtrate was concentrated by evaporation of the solvent under reduced pressure to provide an oil. The oil was dissolved in 120 ml of 3N hydrochloric acid, from which the product as a hydrochloride salt precipitated. The salt so formed was collected by filtration and recrystallized from methanol and toluene to provide 36.2 g of dl-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride. M.P. 195°–197.5° C.

EXAMPLE 4

Resolution of dl-1-methyl-3-(4-benzyloxyphenyl)propylamine to provide R-(−)-1-methyl-3-(4-benzyloxyphenyl)-propylamine

A solution of 629.3 g of dl-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride was converted to the free amine by reaction with 95 g of sodium hydroxide in 400 ml of water. The free amine was then dissolved in 2000 ml of methylene chloride and added to a solution of 328 g of D-(−)-mandelic acid in 1000 ml of methanol. The mandelic acid salt of the free amine precipitated out of solution and was recrystallized three times from methanol to provide 322 g of the R-mandelic acid salt of R-1-methyl-3-(4-benzyloxyphenyl)propylamine. M.P. 166°–167° C. $[\alpha]_D$ −30°, $[\alpha]_{365}$ −119° (MeOH).

The salt so formed was converted to R-1-methyl-3-(4-benzyloxyphenyl)propylamine as the free base by reaction with aqueous sodium hydroxide.

EXAMPLE 5

R,R-N-[2-(4-Benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine

A solution of 93.9 g of R-1-methyl-3-(4-benzyloxyphenyl)propylamine in 500 ml of N,N-dimethylformamide containing 63.0 g of 1-hydroxybenzotriazole and 104.6 g of R-2-(4-benzyloxyphenyl)-2-hydroxyacetic acid was cooled to 0° C. and stirred while a solution of 83.6 g of N,N'-dicyclohexylcarbodiimide in 300 ml of dimethylformamide was added dropwise over one hour. The reaction mixture was stirred for twelve hours at 3° C. and then was diluted with 10 ml of water, stirred for an additional hour, and then cooled to −30° C. in an ice-acetone bath. The reaction mixture was filtered to remove dicyclohexylurea, and then the filtrate was concentrated by evaporation of the solvent under reduced pressure. The concentrated solution was diluted with ethyl acetate and washed with saturated aqueous sodium carbonate solution, with water, with 300 ml of 1N hydrochloric acid, and again with water. The organic layer was dried and the solvent was removed by evaporation under reduced pressure to pro-

vide the product as a white solid. The solid was recrystallized once from acetonitrile and again from methanol to provide 159.7 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)-propylamine. M.P. 145°–148° C. $[\alpha]_D$ −15.9°, $[\alpha]_{365}$ −50.1° (MeOH).

Analysis calc for $C_{32}H_{33}NO_4$.

Theory: C, 77.55; H, 6.71; N, 2.83.

Found: C, 77.04; H, 6.84; N, 2.53.

EXAMPLE 6

R,R-N-[2-(4-Benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine

To a stirred solution of 10.0 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine in 500 ml of freshly distilled tetrahydrofuran under a nitrogen gas atmosphere was added dropwise over thirty minutes 41 ml of 2 molar borane-dimethyl sulfide complex in tetrahydrofuran. The reaction mixture was stirred at 25° C. for twenty hours, and then was heated to reflux and stirred for an additional three hours. After cooling the reaction mixture to 25° C. and stirring for another eighteen hours, the excess borane was decomposed by the slow portion-wise addition of 400 ml of methanol. The solvent was then removed from the reaction mixture by evaporation under reduced pressure to provide the product as an oil. The oil so formed was dissolved in 250 ml of hot methanol, and after concentrating the volume to 125 ml, the product began crystallizing out of solution. The crystalline product was collected by filtration and recrystallized twice from methanol to provide 6.65 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine. M.P. 119°–123.5° C.

The amine so formed was dissolved in methanol and added to a solution of ethereal hydrogen chloride, thereby providing 6.49 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)-propylaminium chloride. M.P. 214.5√–216° C. $[\alpha]_D$ −13.4°, $[\alpha]_{365}$ −30.2° (MeOH).

Analysis calc. for $C_{32}H_{36}NO_3Cl$.

Theory: C, 74.19; H, 7.00; N, 2.70; Cl, 6.84.

Found: C, 74.20; H, 6.98; N, 2.65; Cl, 6.63.

EXAMPLE 7

R,R-1-(4-Hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride, also named as R,R-N-[2-(4-Hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)propylaminium chloride

A mixture of 51.6 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride and 5.0 g of Raney nickel in 2 liters of ethanol and 2 liters of ethyl acetate was stirred at 25° C. for four and one-half hours under a hydrogen atmosphere of 60 psi. The reaction mixture was then filtered to remove the residual Raney nickel, and the filtrate was concentrated to an oil by evaporation of the solvent under reduced pressure, and the oil was crystallized from fresh ethanol and diethyl ether to provide 29.8 g of R,R-N-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)-propylaminium chloride. M.P. 176°–176.5° C. (dec.) $[\alpha]_D$ −22.7°, $[\alpha]_{365}$ −71.2° (3.7 mg/ml MeOH).

Analysis calc. for $C_{18}H_{24}NO_3Cl$.

Theory: C, 63.99; H, 7.16; N, 4.15.

Found: C, 63.70; H, 7.26; N, 4.32.

EXAMPLE 8

As pointed out above, a preferred embodiment of this invention employs a mixture of all four optical isomers of the compound of Example 7. This racemic mixture can be prepared by the method described above by reaction of dl-4-(benzoyloxy)mandelic acid with dl-1-methyl-3-(4-benzyloxyphenyl)propylamine in the presence of DCC to give racemic 1-(4-benzyloxyphenyl)-2-oxo-2-[1-methyl-3-(4-benzyloxyphenyl)propylamino]ethanol. Reduction of the latter compound and subsequent removal of the benzyl groups provides racemic 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]-ethanol. This compound is more preferably prepared by the following procedure.

A solution of 32.8 g. (0.2 m) of methyl 2-(4-hydroxyphenyl)ethyl ketone and 42.6 g. (0.2 m) of 1-(4-hydroxyphenyl)-2-aminoethanol in 380 ml. of ethanol containing 3.8 g. of five percent palladium on carbon was stirred for sixteen hours at 60° C. under hydrogen at 55 psi. The reaction mixture was then filtered, and the filtrate was diluted by addition of 350 ml. of water. The aqueous mixture was concentrated to a volume of about 400 ml., and then washed with dichloromethane. The aqueous mixture was acidified by addition of 50 ml. of conc. hydrochloric acid. After standing at room temperature for two hours, the aqueous acid mixture was filtered and the filter cake was washed with 40 ml. of ice water and dried at 50° C. in vacuum to provide 47 g. of 1-(4-hydroxyphenyl-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride. M.P. 124°–129° C.

Analysis calc. for $C_{18}H_{24}NO_3Cl$.

Theory: C, 63.99; H, 7.16; N, 4.15; Cl, 10.49.

Found: C, 63.77; H, 6.80; N, 3.91; Cl, 10.68. ^{13}C NMR studies demonstrated the product to be comprised of 51% RR,SS diastereamer and 49% RS,SR diastereomer.

EXAMPLE 9

1-Phenyl-2-[1-methyl-3-(4-nitrophenyl)propylamino]ethanol

A solution of 5.0 g. (25.9 mM) of 2-amino-1-phenylethanol and 3.55 g. (25.9 mM) of methyl 2-(4-nitrophenyl)ethyl ketone in 60 ml. of toluene containing 10 mg. of para-toluenesulfonic acid was heated at reflux for six hours in a flask equipped with a Dean-Stark trap. The water that formed during the reaction was removed via the trap, and then the reaction mixture was cooled to room temperature and concentrated to dryness by evaporation of the solvent under reduced pressure. The solid product that remained was dissolved in 50 ml. of tetrahydrofuran and the solution was heated to reflux. A solution of 13.5 ml. of 2N borane-methyl sulfide complex in tetrahydrofuran was then added dropwise to the reaction mixture, and the mixture was refluxed for an additional ninety minutes. After cooling the reaction mixture to room temperature, it was diluted by addition of diethyl ether saturated with hydrogen chloride. The precipitate that was formed was collected by filtration and crystallized from ethanol and diethyl ether to give 3.29 g. of 1-phenyl-2-[1-methyl-3-(4-nitrophenyl)-propylamino]ethanol hydrochloride. M.P. 203°–213° C.

Analysis calc. for $C_{18}H_{23}ClN_2O_3$.

Theory: C, 61.62; H, 6.61; N, 7.98; Cl, 10.11.

Found: C, 61.76; H, 6.62; N, 7.76; Cl, 10.13.

EXAMPLE 10

1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]ethanol

A solution of 32.6 g. (0.2 m) of 1,1-dimethyl-3-phenylpropylamine and 22.9 g. (0.1 m) of 2-(4-methoxyphenyl)-2-oxoethyl bromide in 75 ml. of tetrahydrofuran was heated at reflux for thirty-six hours. The reaction mixture was then cooled and added to 2 liters of diethyl ether. The precipitate was removed by filtration, and the filtrate was acidified with hydrobromic acid to give 18.15 g. of 1-(4-methoxyphenyl)-1-oxo-2-(1,1-dimethyl-3-phenylpropylamino)ethane hydrobromide. M.P. 174°–178° C.

The compound thus formed was dissolved in 85 ml. of glacial acetic acid containing 35 ml. of hydrobromic acid, and the solution was heated at reflux for nine hours. The solution was then cooled and the solvent was removed by evaporation to provide, following crystallization from ethanol and diethyl ether, 7.8 g. of 1-(4-hydroxyphenyl)-1-oxo-2-(1,1-dimethyl-3-phenylpropylamino)ethane hydrobromide. M.P. 228°–230° C.

Catalytic hydrogenation of 5.0 g of the compound from above in 44 ml. of ethanol containing 1.25 g. of five percent palladium on carbon afforded, following crystallization from acetone and diethyl ether, 2.3 g. of 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-phenylpropylamino)ethanol hydrobromide. M.P. 168°–170° C.

Analysis calc. for $C_{19}H_{26}BrNO_2$.
Theory: C, 60.00; H, 6.89; N, 3.68.
Found: C, 60.28; H, 6.67; N, 3.62.

EXAMPLE 11

1-(3-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethanol

To a stirred solution of 67.2 g. (0.22M) of 2-(3-benzyloxyphenyl)-2-oxoethyl bromide in 200 ml. of acetonitrile was added as solution of 54.3 g. (0.20M) of N-benzyl-1,1-dimethyl-3-(4-fluorophenyl)propylamine in 600 ml. of acetontrile containing 42 ml. (0.22M) of diisopropylethylamine. The reaction mixture was stirred for about six hours at reflux, and then was cooled and stored at room temperature for forty-eight hours. The reaction mixture was next diluted by addition of aqueous sodium hydroxide, and the organic solvents were removed by evaporation under reduced pressure. The aqueous alkaline mixture was extracted with ethyl acetate, which was then washed with water, dried, and concentrated to dryness to give an oil. The oil was dissolved in ethanol and diethyl ether and converted to the hydrochloride salt by addition of excess hydrogen chloride. The precipitated solid was collected by filtration and recrystallized from ethyl acetate to give 51.3 g. of 1-(3-benzyloxyphenyl)-1-oxo-2-[(N-benzyl)-1,1-dimethyl-3-(4-fluorophenyl)-propylamino]ethane hydrochloride. M.P. 137°–145° C.

The compound thus prepared was reduced by reaction with 16 g. of sodium borohydride in ethanol. Isolation of the product, followed by conversion to the hydrochloride salt and crystallization from diethyl ether afforded 55.0 g. of 1-(3-benzyloxyphenyl)-2-[(N-benzyl)-1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethanol hydrochloride. M.P. 186.5°–191° C.

A solution of 10.0 g. of the product thus produced in 200 ml. of ethanol containing 3.0 g. of Raney Nickel was shaken for two hours at 25° C. under hydrogen at 44 psi. The reaction mixture was then filtered, and the solvent was removed from the filtrate by evaporation under reduced pressure to give a white solid. The solid was triturated with ethyl acetate and air dried to provide 5.9 g. of 1-(3-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethanol hydrochloride. M.P. 196.5°–198.5° C.

Analysis calc. for $C_{19}H_{25}ClFNO_2$.
Theory: C, 64.49; H, 7.12; N, 3.96; Cl, 10.02.
Found: C, 64.29; H, 6.97; N, 4.06; Cl, 9.89.

EXAMPLE 12

1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol

A suspension of 10.0 g. (50 mM) of 1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamine and 15.0 g. (50 mM) of 1-(4-benzyloxyphenyl)-1-oxoethyl bromide in 1000 ml. of acetonitrile containing 32.0 g. (0.3M) of sodium carbonate and 100 ml. of water was stirred for one hour at 25° C. The precipitate that formed was collected by filtration, washed with water and with diethyl ether, and air dried to provide 8.0 g. of 1-(4-benzyloxyphenyl)-1-oxo-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)-propylamino]ethane. M.P. 184°–187° C. This product was converted to the hydrochloride salt by reaction with hydrogen chloride in diethyl ether. M.P. 219°–224° C.

The compound thus prepared was reacted with sodium borohydride in methanol to provide, following conversion to the hydrochloride salt and crystallization from methanol and diethyl ether, 5.8 g. of 1-(4-benzyloxyphenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride. M.P. 141°–143° C.

Reaction of the above compound with hydrogen in the presence of Raney Nickel effected cleavage of the hydroxy protecting group to afford, following crystallization of the hydrochloride salt, 1.3 g. of 1-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride. M.P. 185° C. (dec.)

Analysis calc. for $C_{20}H_{27}ClN_2O_3$.
Theory: C, 63.40; H, 7.18; N, 7.39; Cl, 9.36.
Found: C, 63.26; H, 7.01; N, 7.45; Cl, 9.42.

The compounds of Examples 13 and 14 were prepared by the general procedure of Example 12.

EXAMPLE 13

1-(2-Fluorophenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride

M.P. 227°–230° C.

EXAMPLE 14

1-(3-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrobromide

M.P. 161°–165° C.

EXAMPLE 15

1-Phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl)-propylamino]ethanol hydrochloride

Methyl 2-(4-methylthiophenyl)ethyl ketone was oxidized by reaction with m-chloroperbenzoic acid to give methyl 2-(4-methylsulfonylphenyl)ethyl ketone. A solution of 6.73 g. of 2-amino-1-phenylethanol and 11.10 g. of methyl 2-(4-methylsulfonylphenyl)ethyl ketone in 500 ml. of toluene containing 200 mg. of p-toluenesulfonic acid was heated at reflux for twenty-four hours. The reaction mixture was cooled and the solvent was

removed by evaporation to give the Schiff base 1-phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl)-propylamino]ethanol. The Schiff base thus prepared was reacted with 3.7 g. of sodium borohydride in 500 ml. of ethanol at 0° C. for sixteen hours. The reaction mixture was diluted by addition of 50 ml. of acetone and 20 ml. of 3N hydrochloric acid. The mixture was concentrated to an oil by evaporation of the solvent. The oil crystallized upon standing at room temperature. Recrystallization of the product from 200 ml. of hot ethanol afforded 8.96 g. (48% yield) of 1-phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl)propylamino]ethanol hydrochloride. M.P. 164°–170° C.

Analysis calc. for $C_{19}H_{26}ClNO_3S$.

Theory: C, 59.44; H, 6.83; N, 3.65; Cl, 9.23; S, 8.35.

Found: C, 59.28; H, 6.57; N, 3.70; Cl, 9.36; S, 8.11.

Ingredient	% by weight
Example 16 **Premix for Chickens**	
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]-ethanol succinate	25
Ground Corn	74
Sodium Chloride	1
	100
Example 17 **Premix for ruminants**	
1-(2-fluorophenyl)-2-[1,1-dimethyl-3-(4-aminocarbonyl-phenyl)propylamino]ethanol	30
Ground yellow corn	60
Alfalfa meal	10
	100
Example 18 **Premix for Swine**	
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol hydrochloride	10
Soybean mill run	88
Mineral oil	2
	100

The above ingredients are blended to uniformity to provide a dry flowable premix that can be admixed with a typical animal feed ration at a rate to provide about 20 ppm of active ingredient in the final feed ration. For example, the premix can be added to the following swine grower ration for convenient oral administration of the β-phenethanolamine to swine.

Ingredient	% by weight	lbs/Ton
Corn, yellow, ground	76.70	1534
Soybean Oil Meal, solvent extracted, dehulled	19.35	387
Calcium Carbonate	1.20	24
Dicalcium Phosphate, feed grade	1.20	24
Salt (sodium chloride)	0.50	10
Trace mineral premix, AN-03[1]	0.10	2
Swine Vitamin Premix, SW-03[2]	0.65	13
Vitamin A Premix, 3M USP units/lb.[3]	0.05	1
Methionine Hydroxy Analogue, 93%	0.20	4
Selenium Premix[4]	0.005	1
	100.00	2000

[1]Each Kg of premix contains: 50 g. manganese as manganese sulfate; 100 g. zinc as zinc carbonate; 50 g. iron as ferrous sulfate; 5 g. copper as copper oxide; 1.5 g. iodine as potassium iodine and 150 g. maximum and 130 g. minimum calcium as calcium carbonate.

[2]Each Kg of premix contains: 77,161 IU Vitamin D_3; 2,205 IU Vitamin E; 411 mg. riboflavin; 1,620 mg. pantothenic acid; 2,205 mg. niacin; 4.4 mg. Vitamin B_{12}; 441 mg. Vitamin K; 19,180 mg. choline; 110 mg. folic acid; 165 mg. pyridoxine; 110 mg. thiamine; 22 mg. biotin.

[3]Each Kg of premix contains 6,613,800 IU Vitamin A.

[4]Each Kg of premix contains 200 mg. of selenium as sodium selenite.

Example 19
Feed Ration for Lambs

Ingredient	Percent	lbs/T
Yellow corn	61.00	1220.0
Corn cobs	20.00	400.0
Alfalfa Meal, dehydrated	5.40	108.0
Soybean oil meal	8.00	160.0
Urea, feed grade	0.50	10.0
Molasses, cane	3.00	60.0
Dicalcium phosphate	0.43	8.6
Salt	0.30	6.0
Calcium carbonate	0.14	2.3
Trace mineral premix[1]	0.03	0.6
Vitamin A + D_3 Premix[2]	0.10	2.0
Vitamin E Premix[3]	0.10	2.0
1-(4-Hydroxyphenyl)-2-(1,1-dimethyl-3-phenylpropylamino)-ethanol	1.00	20.0
	100.00	2000.00

[1]Trace mineral premix contains: 2.5% manganese as manganese oxide, 0.07% iodine as potassium iodide, 0.3% cobalt as cobalt carbonate, 0.5% copper as copper oxide, and 20.0% zinc as zinc sulfate.

[2]Each pound of vitamin A and D_3 premix contains 2,000,000 USP units Vitamin A and 225,750 USP units Vitamin D_3.

[3]Each pound of Vitamin E premix contains 20,000 IU Vitamin E.

The compounds to be employed in the method of this invention have demonstrated efficacy in animal tests designated to establish beneficial nutritional effects. In one test designed to show lipolytic activity, normal swine, either barrows or gilts, were employed to analyze the effect of compounds on blood glucose, insulin, and non-esterified fatty acids (NEFA).

Test animals were maintained in metabolism crates, and following a period of adaptation, catheters were placed in their femoral veins. Prior to administration of the test compounds, all animals were fasted for a period of forty hours. Such fasting causes an elevation of NEFA's in the blood. On the day of the test, all animals were fed a normal feed ration, and one group of animals were held as controls while another group of animals received a test compound. The test compounds were administered at 200 mcg/kg intravenously, or orally at 1 mg/kg. Blood samples were taken from each animal immediately prior to treatment and then at one hour intervals for a period of six hours following treatment. The blood plasma was analyzed for glucose, insulin and NEFA content.

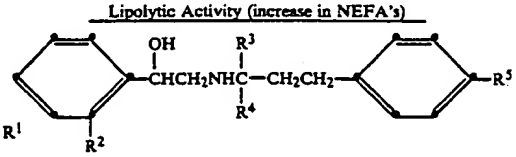
When the fasted pigs were fed the normal feed ration without a test compound, the NEFA levels in the blood drop dramatically and remained low. A β-phenethanolamine as defined herein caused either an elevation in NEFA's, or inhibited the drop in NEFA's. Blood levels of glucose and insulin were also elevated with the β-phenethanolamines.

The following Table presents the lipolytic activity of several preferred β-phenethanolamines when evaluated

according to the test described above. The results are averages of several tests.

TABLE I

Lipolytic Activity (increase in NEFA's)



R^1	R^2	R^3	R^4	R^5	% increase in NEFA's over control	% increase in glucose over control
H	H	H	CH_3	SO_2CH_3	131	9
p-OH	H	CH_3	CH_3	H	445	48
m-OH	H	CH_3	CH_3	H	71	31
m-OH	H	CH_3	CH_3	F	28	72
p-OH	H	CH_3	CH_3	OH	141	35
p-OH	H	CH_3	CH_3	$CONH_2$	18	169
m-OH	H	CH_3	CH_3	OH	68	40
H	H	H	H	NO_2	199	7
p-OCH_3	H	CH_3	CH_3	H	84	25
p-OCH_3	H	CH_3	CH_3	OH	249	5
H	H	H	CH_3	NO_2	1458	27

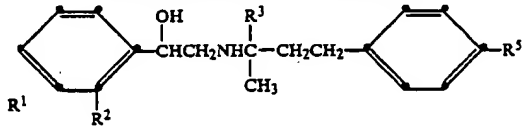
A ten day in vivo study was employed to determine the effect of β-phenethanolamines on feed efficiency and rate of growth. In these studies, barrows and gilts weighing approximately 60 kg were maintained in individual pens. Each treatment was replicated six times in randomly assigned animals, with each test animal forming an experimental unit. A group of control animals received a normal swine grower feed ration comprising the following ingredients:

Ingredient	% by weight
Ground yellow corn	76.70
Soybean oil meal	19.35
Calcium carbonate	1.20
Dicalcium phosphate	1.20
Salt	0.50
Trace mineral premix	0.10
Swine Vitamin premix	0.65
Vitamin A premix, 3M USP units/lb.	0.05
Methionine Hydroxy analogue, 93%	0.20
Selenium premix	0.05
	100.00

The test animals received the same feed ration plus the test compound. All animals received feed and water ad libitum. All animals were weighed on day 1 and again on day 10, and feed consumption was measured by recording all feed issued and any remaining feed on day 10. The results of two series of this 10 day test for several β-phenethanolamines are given in Table II. In the Table, the column labelled "ADG" is the average daily weight gain in pounds; "ADF" is the average daily feed consumption (in pounds) by the test animals; and F/G is the feed efficiency calculated as ADF divided by ADG.

TABLE II

Growth Promotion and Feed Efficiency



	R^1	R^2	R^3	R^5	dose ppm	ADG	ADF	F/G
Experiment I	Control					1.60	4.7	2.98
	p-OH	H	H	OH	20	2.19	5.0	2.33
	H	H	H	NO_2	20	1.78	4.22	2.37
Experiment II	Control					1.34	4.16	3.22
	p-OH	H	CH_3	H	20	1.60	4.26	2.66
	m-OH	H	CH_3	F	20	1.52	4.57	3.01

The β-phenethanolamines to be employed in the method of this invention can be administered in combination with other compounds known to have a beneficial effect upon animals. Typical compounds to be coadministered with the β-phenethanolamines include antibiotics, for example any of the tetracyclines, tylosin, penicillins, cephalosporins, polyether antibiotics, glycopeptides, orthosomycins and related compounds commonly administered to swine, poultry, ruminants and the like. A preferred combination to be employed in the present method is an antibiotic such as tylosin or a tetracycline, together with 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol. Such combinations will comprise the respective components in a ratio of about 1 to about 2 parts by weight of β-phenethanolamine and about 1 to about 10 parts by weight of the partner component.

In a typical treatment, 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol was evaluated in a 42-day study employing finishing swine. Each treatment was replicated four times, with three pigs per replication. All treatments included a normal feed diet plus tylosin at 40 g/T. The animals were tested for growth performance and feed efficiency enhance-

ment. Carcass quality was determined by analysis for fat and muscling. The results of the study are given in Table III. Both β-phenethanolamine treatments resulted in improved growth performance and carcasses with less fat and more muscle.

TABLE III

	Growth Promotion, Feed Efficiency and Carcass Quality				
		β-phenethanolamine[2]			
	Control[1]	20 g/T	% change	40 g/T	% change
ADG	1.94	2.07	(6.7)	2.05	(5.7)
ADF	6.28	6.63	(5.6)	6.64	(5.7)
F/G	3.24	3.20	(−1.2)	3.24	(0)
Live Wt. at Slaughter, lb	217.0	223.0	(2.8)	221.0	(1.8)
Chilled Carcass Wt., lb	154.6	160.5	(3.8)	159.8	(3.4)
Fat Depth at 10th Rib, in	1.15	1.09	(−5.2)	1.05	(−8.7)
Loin Eye Area Sp., in	4.64	4.91	(5.8)	4.84	(4.3)
Estimated pounds of Fat Free Muscle[3]	74.2	78.8	(6.1)	78.4	(5.7)

[1]all diets contained 40 g/T of tylosin
[2]l-(4-hydroxyphenyl)-2-[l-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol hydrochloride
[3]A regression equation was employed in arriving at the numerical predictions of carcass muscle (J. Animal Science, 1977, Vol. 44:8–17).

The data reported in Table III further demonstrates that the β-phenethanolamines described herein promote growth, improve feed efficiency and improve leaness.

In a similar study conducted over a 61 day period, a group of control animals received a normal daily feed ration with no additive. Another group of animals received the feed ration plus tylosin at 40 g/T, while another group received the feed ration plus 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride (compound A) at 20 g/T. A final group of finishing swine received the feed ration plus the combination of 40 g/T of tylosin and 20 g/T of the phenethanolamine. The results of this trial are given in Table IV.

TABLE IV

	Control	Tylosin	A	Tylosin +A
ADG	1.63	1.64	1.36	1.50
ADF	5.64	5.77	5.10	5.38
F/G	3.46	3.51	3.77	3.59
Slaughter Wt, (lbs)	210	211	193	201
Carcass Wt, (lbs)	150.3	151.5	140.1	146.3
Fat Depth, 10th rib, (in)[1]	0.96	0.96	0.80	0.85
Loin Eye Area (in^2)[1]	4.60	4.68	4.92	5.00
Est. % Muscle[2]	49.2	49.2	51.4	51.2
Est. Pounds Muscle[2]	75.3	76.5	74.1	76.8

[1]These results are based upon measurement of fat at the 10th rib after the carcass is split in half across the backbone.
[2]A regression equation is employed in arriving at the numerical predictions of carcass muscle (J. Animal Science, 1977, Vol. 44:8–17).

As in the previous study, both phenethanolamine treatments resulted in carcasses with less fat and more muscle. Is should also be noted that the estimated amount of carcass muscle produced with the Tylosin +A treatment was similar to that produced in the control and the Tysolin treatment alone. This result was achieved, however, with less feed consumption than either the control or the Tylosin treatments.

Additional studies have been carried out to demonstrate the anabolic effect of β-phenethanolamines in swine. The effect of the compounds on nitrogen retention in finishing barrows was determined. Nitrogen retention is the difference between nitrogen intake and nitrogen excreted. Increased nitrogen retention is known to be associated with increased anabolic activity, resulting in improved carcass muscling and leanness.

In a typical study, barrows weighing about 172 pounds (78 Kg) were orally administered various doses of 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride (Compound A). All animals received water and a constant amount of normal swine feed ration. The results of this study are presented in Table V, and show that all β-phenethanolamine treatments improved nitrogen retention compared to controls.

TABLE V

Treatment	Nitrogen Retention Animals per treatment	Nitrogen Retained (g/day)
Control	6	21.0
Compound A (5 g/T)	3	23.6
Compound A (10 g/T)	3	23.9
Compound A (20 g/T)	3	25.0

As pointed out above, the method of this invention can be practiced with individual isomers of β-phenethanolamines or with mixtures of isomers and diastereomers. In a study to determine the effect on weight gain and feed efficacy of various mixtures of diastereomers, barrows initially weighing about 177 pounds were fed a normal swine diet plus a β-phenethanolamine at 20 g/T of feedstuff. Each treatment was replicated in twelve individually fed animals. The results are presented in Table VI and show that growth performance was improved by both β-phenethanolamine treatments with very little change in feed intake.

TABLE VI

Treatment	Average Daily Feed (lbs)	Average Daily Gain (lbs)
Control	5.89	1.58
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride 57.5% RR,SS 42.5% RS,SR	5.94	2.15
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride 47% RR,SS 53% RS,SR	5.86	1.95

The data in Table VI demonstrates that the method of improving feed efficiency and promoting growth can be practiced with any desired mixture of β-phenethanolamine optical isomers.

The efficacy of the β-phenethanolamines described herein also has been demonstrated in poultry. In a typical study, broilers that were twenty-one days old were administered an oral dosing of a β-phenethanolamine in their normal daily feed ration. All animals received the following broiler finisher ration:

Ingredients	% by weight	lbs/T
Ground yellow corn	66.40	1328.00
Animal-vegetable fat	1.53	30.60
Corn Glut. meal (60%)	4.00	80.00
Soybean meal (48%)	19.19	383.80
Fish meal-menhaden	2.50	50.00

-continued

Ingredients	% by weight	lbs/T
Dicalcium phosphate	1.01	34.20
Feather meal-Hydr.	2.50	50.00
Ground limestone	0.83	16.60
Salt	0.30	6.00
Vitamin Premix[1]	0.50	10.00
Trace mineral premix[2]	0.10	2.00
Methionine Hyd. Anal.	0.15	3.00
Lysine HCl	0.29	5.80
	100.00	2000.00

[1]Vitamin premix provides 3000 IU of vitamin A, 900 ICU of vitamin D_3, 40 mg. of vitamin E, 0.7 mg. of vitamin K, 1000 mg of choline, 70 mg. of niacin, 4 mg of pantothenic acid, 4 mg of riboflavin, 100 mcg of vitamin B_{12}, 100 mcg of biotin and 125 mg of ethoxyquin per kg of complete feed.

[2]Trace mineral premix provides 75 mg of manganese, 50 mg of zinc, 25 mg of iron and 1 mg of iodine per kg of complete feed.

Test animals received with the above ration varying doses of 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride (compound A). Each treatment was replicated sixteen times, and the test was terminated when the animals reached fifty-six days of age. The animals were analyzed for weight gain and feed efficiency. The results of this test in broilers is presented in Table VII as mean weight gain and mean feed to gain ratios.

TABLE VII

		Growth Performance of Broilers			
		Weight Gain		Feed Efficiency	
Treatment	Dose (g/T)	grams	% improvement	Feed/ Gain Ratio	% change from control
Control		1473	0	2.336	0
Compound A	10	1585	7.6	2.292	1.9
Compound A	20	1613	9.5	2.298	1.6
Compound A	40	1550	5.2	2.312	1.0
Compound A	80	1669	13.3	2.221	4.9

TABLE VII-continued

		Growth Performance of Broilers			
		Weight Gain		Feed Efficiency	
Treatment	Dose (g/T)	grams	% improvement	Feed/ Gain Ratio	% change from control
A					

The results of this study demonstrates that the β-phenethanolamines described herein are effective in promoting growth and improving feed efficiency in poultry.

The compounds of the invention also have demonstrated efficacy in ruminants. Forty-eight cross-bred wether lambs were employed in a test designed to show the effects of Compound A (1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride) at varying doses. Sixteen animals were held as controls, while sixteen received 40 ppm of Compound A, and another sixteen received 80 ppm of Compound A. All animals received a normal daily feed ration and water ad libitum. Average daily weight gain and average daily feed consumption after twenty-eight days is given below in Table VIII. The data demonstrates that a β-phenethanolamine as defined herein is effective in promoting growth and improving feed efficiency in ruminants.

TABLE VIII

	Growth Performance of Lambs			
Treatment	Dose (ppm)	ADG (lbs)	ADF (lbs)	F/G
Control	0	0.414	3.68	8.89
Compound A	40	0.418	3.61	8.64
Compound A	80	0.472	3.57	7.56

We claim:

1. An improved method of raising a meat producing animal which comprises administering to the animal a growth promoting, feed efficiency improving, or carcass quality improving amount of 1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]ethanol or an acid addition salt thereof.

2. An animal feedstuff comprising 1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]ethanol or an acid addition salt thereof together with a suitable carrier therefor.

* * * * *

Exhibit XIII

U.S. Patent 4,992,473

United States Patent [19]

Anderson et al.

[11] **Patent Number: 4,992,473**

[45] **Date of Patent: * Feb. 12, 1991**

[54] **GROWTH PROMOTION**

[75] Inventors: **David B. Anderson**, Greenfield; **Klaus K. Schmiegel**, Indianapolis; **Edward L. Veenhuizen**, Greenfield, all of Ind.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[*] Notice: The portion of the term of this patent subsequent to Mar. 29, 2005 has been disclaimed.

[21] Appl. No.: **328,996**

[22] Filed: **Mar. 27, 1989**

Related U.S. Application Data

[60] Division of Ser. No. 153,640, Feb. 8, 1988, Pat. No. 4,849,453, which is a division of Ser. No. 860,719, May 7, 1986, Pat. No. 4,734,437, which is a continuation of Ser. No. 628,002, Jul. 5, 1984, abandoned, which is a continuation of Ser. No. 462,587, Jan. 31, 1983, abandoned.

[51] **Int. Cl.**[5] **A61K 31/135**

[52] **U.S. Cl.** **514/653**

[58] **Field of Search** 514/620, 653

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,391,826 7/1983 Mills et al. 424/324

FOREIGN PATENT DOCUMENTS

49728 4/1982 European Pat. Off. .

OTHER PUBLICATIONS

J. Pharm. Pharmacol., 18(3), 188-189 (1966), "The Effects of Some Derivatives of Noradrenaline and 2-Amino-1-p-hydroxy-Phenylethanol on the In Vitro Mobilization of Fat".

Primary Examiner—Frederick E. Waddell
Attorney, Agent, or Firm—Donald R. Stuart; Leroy Whitaker

[57] **ABSTRACT**

β-Phenethanolamines are effective in promoting growth and improving feed efficiency and leanness in animals.

8 Claims, No Drawings

GROWTH PROMOTION

This application is a division of Ser. No. 07/153,640, Feb. 8, 1988, U.S. Pat. No. 4,849,453, which is a division of Ser. No. 860,719, May 7, 1986, U.S. Pat. No. 4,734,437, which is a continuation of Ser. No. 628,002, July 5, 1984, abandoned, which is a continuation of Ser. No. 462,587, Jan. 31, 1983, abandoned.

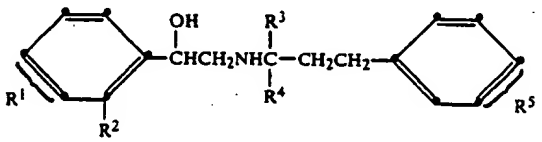
BACKGROUND OF THE INVENTION

The chemistry and use of β-phenethanolamines has been extensively investigated. A number of these compounds have been reported to have beneficial cardiac activities; see U.S. Pat. No. 3,987,200. Such compounds also are known to have sympathomimetic activity, and have found utility as utero-relaxing agents; Van Dijk et al., *Recueil,* 92, 1281 (1973). More recently, a group of β-phenethanolamines have been reported as possessing anti-hyperglycemic activity, and have been found effective in promoting the loss of weight in animals, EPO No. 6735 published Jan. 9, 1980.

An object of this invention is to provide a new use for certain β-phenethanolamines. This invention provides a method for promoting the growth of domesticated animals employing β-phenethanolamines.

SUMMARY OF THE INVENTION

This invention provides a method for increasing weight gain in animals and improving the efficiency of feed utilization and the quality of the carcass. The invention is more particularly directed to a method for promoting growth and improving feed efficiency and leanness comprising administering an effective amount of a compound having the formula



wherein:

R^1 is hydrogen, hydroxy, or methoxy;

R^2 is hydrogen or fluoro,

R^3 is hydrogen or C_1-C_2 alkyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, fluoro, nitro, hydroxy, SO_2CH_3 or $CONH_2$; provided that R^1 is hydrogen only when R^5 is nitro or SO_2CH_3; and the acid addition salts thereof.

A preferred method for promoting growth and improving feed efficency and leanness according to this invention employs a compound of the above formula wherein R^1 is hydroxy, R^2 is hydrogen, R^3 is hydrogen or methyl and R^4 is methyl The method is most preferably practiced employing a compound wherein R^1 and R^5 both are hydroxy and R^2 and R^3 both are hydrogen and R^4 is methyl. When R^1 is hydroxy or methoxy, it preferably is in the para position. When R^5 is other than hydrogen, it also is preferably in the para position.

This invention also provides an animal feedstuff comprising a β-phenethanolamine of the above formula together with a suitable carrier therefor.

DETAILED DESCRIPTION OF THE INVENTION

The compounds employed in the method provided by this invention are either known in the art or are readily prepared by well known synthetic procedures. A particularly preferred method employs 1(3-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]-ethanol. This β-phenethanolamine is disclosed in South African Patent No. 673,994 published in May, 1967. The most preferred embodiment of this invention employs 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol, a compound disclosed as having utero-relaxing activity by Van Dijk et al. in *Recueil,* 92 1281 (1973).

The compounds to be employed in the method of this invention are readily prepared by reaction of a styrene oxide with a 3-phenylpropylamine derivative. For example, a styrene oxide such as 2-fluorostyrene oxide can be reacted with about an equimolar quantity of an amine such as 1-methyl-3-(4-nitrophenyl)propylamine in an unreactive organic solvent such as ethanol, methanol, n-propanol, dioxane, or the like. The reaction generally is carried out at a temperature of about 50° to about 120° C., and at such temperature the reaction routinely is substantially complete within about 6 to about 10 hours. The product, a β-phenethanolamine, is readily isolated by simply removing the reaction solvent, for instance by evaporation under reduced pressure, and further purification can be accomplished if desired by standard techniques, including crystallization, chromatography, acid-base extraction, and the like.

An alternative method for preparing the β-phenethanolamines to be employed in the present method comprises reacting a mandelic acid derivative with a 3-phenylpropylamine derivative to provide an amide, which upon subsequent reduction provides a compound of the above formula. For example, a phenylpropylamine derivative such as 1-methyl-3-(3-fluorophenyl)-propylamine can be reacted with an acylating agent such as a hydroxy protected mandelic acid halide, or preferably simply reacted with a mandelic acid in the presence of a common peptide coupling reagent such as N,N'-dicyclohexylcarbodiimide, carbonyldiimidazole, N-ethoxy- carbonyl-2-ethoxy-1,2-dihydroquinoline, commonly referred to as EEDQ. The direct coupling reaction generally is conducted in an organic solvent such as benzene or N,N-dimethylformamide, and normally is complete after about 2 to 48 hours when carried out at about −30° to about 100° C. The product is an amide that is readily isolated by simply filtering the reaction mixture and then removing the reaction solvent. The amide thus formed is next reduced by reaction with a common reducing agent such as diborane or the like to provide a β-phenethanolamine defined by the above formula.

A similar, yet alternative, method of synthesis comprises reacting a phenethanolamine with a phenylethyl ketone to provide a Schiff base, which upon reduction gives a compound to be employed in the present method. For example, a phenethanolamine such as 2-hydroxy-2-(4-hydroxyphenyl)ethylamine can be reacted with a ketone such as methyl 2-(4-hydroxyphenyl)ethyl ketone to provide the corresponding imine, which upon reduction, for instance with 5% palladium on carbon, provides 1-(4-hydroxyphenyl)-2[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol.

It should be noted that the compounds to be employed in the method of this invention possess at least one asymmetric center (i.e. the carbinol center), and when R^3 and R^4 differ, the compounds possess two asymmetric centers. Since employment of individual optical isomers necessitates preparing the β-phenethanolamines from optically active starting materials, or using costly separation procedures, a preferred embodiment of this invention employs a mixture of optical isomers. For example, 1-(4-hydroxyphenyl)2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol is preferably prepared from racemic mixtures of starting materials, e.g. dl-1-methyl-3-(4-hydroxyphenyl)propylamine and dl-4-hydroxystyrene oxide, to provide a mixture of all four possible optical isomers of the product. The mixture of optical isomers is employed in the method without subsequent separation of isomers.

Since the β-phenethanolamines to be employed in the present method are inherently basic, they readily form acid addition salts with any number of inorganic and organic acids. These salts can be employed in the method of the invention, and often are preferred to the free base since they generally are more soluble in solvents such as water and are more conveniently formulated as an animal feedstuff. Acids commonly employed to form acid addition salts include mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid, perchloric acid and the like; and organic acids such as acetic acid, citric acid, succinic acid, para-toluene acid, methanesulfonic acid, lactic acid and the like. Preferred salts to be employed in the present method include the hydrochlorides and hydrobromides.

Typical β-phenethanolamines to be employed in the method of this invention include the following:

1-(3-hydroxyphenyl)-2-[1-methyl-1-ethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol;
1-(2-fluoro-4-hydroxyphenyl)-2-[1-methyl-3-(4-fluorophenyl)propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[3-(3-nitrophenyl)-propylamino]ethanol;
1-(3-hydroxy-2-fluorophenyl)-2-[3-(4-methylsulfonyl)propylamino]ethanol;
1-(4-methoxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol;
1-phenyl-2-[1,1-dimethyl-3-(3-methylsulfonyl-phenyl)propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride;
1-(phenyl)-2-[1-methyl-3-(4-nitrophenyl)-propylamino]ethanol; phenyl)propylamino]ethanol succinate;
1-(4-hydroxyphenyl)-2-[1-methyl-1-ethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol;
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-phenyl-propylamino]ethanol hydrobromide; and
d-1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol.

The method of promoting growth and improving leanness and feed efficiency provided by this invention is practiced by administering an effective amount of a compound defined above to a warm-blooded animal that receives a nutritionally adequate diet. The method generally will be practiced on domesticated animals raised for human meat consumption, for example grower/finisher swine, poultry, ruminants and the like. In a preferred embodiment, the growth of pigs, chickens and turkeys is promoted employing a β-phenethanolamine. Another preferred embodiment is practiced in ruminants such as cattle, sheep and goats. The method of improving leanness is not limited to meat producing animals, and can be practiced on other warm-blooded animals, including dogs and cats. This latter embodiment is particularly useful when it is desired to maintain mature animals in a relatively lean physical state.

The method of the invention is preferably practiced by orally administering an effective amount of a β-phenethanolamine to an animal. Other routes of administration can be employed, for instance intramuscular or intravenious injection; however, such routes are less practical. The amount to be administered to an animal is an amount that is effective in causing a promotion of growth, or an improvement in the efficiency of utilization of food, or an improvement in carcass quality of the animal, for instance in the form of less fatty tissue and improved leanness. The effective amount to be administered will vary somewhat depending upon the particular animal species being treated and the particular active ingredient employed, but generally will be from about 1 to about 1000 parts per million (ppm) of total daily feed intake. Such amount will provide a dosage of about 0.05 to about 50 mg/kg. A preferred embodiment employs about 1 to about 200 ppm, and more preferably from about 5 to about 100 ppm. A typical amount of active ingredient to be administered to swine will be from about 5 to about 40 ppm. For example, when practicing the method in animals such as ruminants or swine, the compound will be added to the daily feed ration at about 5 to about 100 parts per million of the daily feed ration.

For oral administration, the active β-phenethanolamine is preferably admixed with suitable carriers or diluents commonly employed in animal husbandry. Animal feedstuffs comprising a β-phenethanolamine growth promoter as defined herein are provided as a further embodiment of this invention. Typical carriers and diluents commonly employed in such feedstuffs include corn meal, soybean meal, alfalfa meal, rice hulls, soybean mill run, cottonseed oil meal, bone meal, ground corn, corncob meal, sodium chloride, urea, cane molasses and the like. Such carriers promote a uniform distribution of the active ingredient in the finished feed ration into which such compositions are added, thereby ensuring proper distribution of the active ingredient throughout the feed. The feedstuff composition provided by the invention will contain about 5 to about 95 percent by weight of active ingredient, and more typically about 10 to about 50 percent by weight. As already noted, the acid addition salts of the active phenethanolamines are generally preferred for oral administration, and are thus the preferred form of active ingredient for the feedstuff compositions of the invention.

While the preferred method for orally administering the growth promoters is via the daily feed rations, the compounds can be incorporated into salt blocks and mineral licks, as well as being added directly to drinking water for convenient oral consumption. The compounds can additionally be formulated with polymorphous materials, waxes and the like for long-term controlled release, and administered to an animal as a bolus or tablet only as needed to maintain the desired daily payout of active ingredient.

For parenteral administration, the β-phenethanolamines can be admixed with conventional carriers such as corn oil, sesame oil, carbowax, calcium stearate and the like. Such formulations can be molded into pellets and administered as an injection or as a slow-release

subcutaneous implant. Such administrations can be made as often as needed to ensure the proper dosing of active ingredient to obtain the desired rate of growth promotion and improvement in leanness and feed efficiency.

While the compounds described herein are effective in promoting average daily weight gain and improving feed efficiency in animals, they also cause observable improvement in the quality of the meat produced. For example, the compounds appear to mobilize free fatty acids from fatty tissue and depress the deposition of fat as the animals gain weight. This reduction of fat is beneficial since the animal being treated according to the invention gains weight in the form of more useable lean meat, thereby reducing waste and improving the value of the animal thus treated. Also, mature animals that are not subject to additional weight gain can be maintained in a desirably lean form by administering a compound as described herein.

The practice of the present invention is more fully illustrated by the following detailed examples.

EXAMPLE 1

Preparation of dl-4-(benzyloxy)mandelic acid

A solution of 5.0 g of dl-4-hydroxy mandelic acid, 11.0 g of benzyl chloride and 10.0 g of potassium carbonate in 50 ml of methanol was heated to reflux and stirred for seventy-two hours. The reaction mixture was cooled to room temperature and diluted with 50 ml of water. The aqueous solution was washed twice with 50 ml portions of benzene, and then was acidified with concentrated hydrochloric acid. The aqueous acid solution was extracted three times with 50 ml portions of ethyl acetate. The organic extracts were combined, washed with water and with saturated sodium chloride solution and dried. Removal of the solvent by evaporation under reduced pressure provided 5.7 g of a solid which was then recrystallized from 300 ml of toluene to afford 5.33 g of dl-4-(benzyloxy)mandelic acid. M. P. 153°-155° C.

Analysis calc. for $C_{15}H_{14}O_4$: Theory: C, 69.76; H, 5.46; Found: C, 69.96; H, 5.33.

EXAMPLE 2

Resolution of dl-4-(benzyloxy)mandelic acid to provide R(-)-(4-benzyloxy)mandelic acid

To a stirred solution of 185.6 g of dl-4-(benzyloxy)-mandelic acid in 2500 ml of ethyl acetate at 80° C. was added in one portion 43.6 g of R(+)-α-methylbenzylamine. The reaction mixture was cooled to room temperature, and the precipitated solid which had formed was collected by filtration and washed with fresh ethyl acetate. The solid was recrystallized twice from a solution of ninety percent ethanol in water to provide 91.4 g of the R(+)-α-methylbenzylamine salt of R(−)-4-(benzyloxy)mandelic acid. M. P. 208.5°-209.5° C. $[\alpha]_D$−38.6°, $[\alpha]_{365}$−155.3° (MeOH)

Analysis calc. for $C_{23}H_{25}NO_4$: Theory: C, 72.80; H, 6.64; N, 3.69; Found : C, 72.95; H, 6.83; N, 3.95.

To a stirred suspension of 91.4 g of the above-named salt in 2000 ml of ethyl acetate was added 150 ml of ten percent aqueous hydrochloric acid solution. The aqueous acid solution was separated, and the organic layer washed with water and dried. Removal of the solvent by evaporation under reduced pressure afforded 54.5 g of R(−)-4-(benzyloxy)mandelic acid, ie. R(−)-2-(4-benzyloxyphenyl)-2-hydroxyacetic acid. M. P. 155°-161° C. $[\alpha]_D$−102.2°; $[\alpha]_{365}$−410.6° (MeOH)

Analysis calc. for $C_{15}H_{14}O_4$: Theory: C, 69.76; H, 5.46; Found: C, 69.67; H, 5.41.

EXAMPLE 3

Preparation of dl-1-methyl-3-(4-benzyloxyphenyl)propylamine

A solution of 40.0 g of methyl 2-(4-benzyloxyphenyl-)ethyl ketone and 160 ml of anhydrous ammonia in 300 ml of ethanol was heated at 75° C. and stirred for two hours. After cooling the reaction mixture to room temperature, 4.0 g of Raney nickel was added in one portion, and the reaction mixture then was stirred at 25° C. for twelve hours under a hydrogen atmosphere at 300 psi. The reaction mixture next was filtered and the filtrate was concentrated by evaporation of the solvent under reduced pressure to provide an oil. The oil was dissolved in 120 ml of 3N hydrochloric acid, from which the product as a hydrochloride salt precipitated. The salt so formed was collected by filtration and recrystallized from methanol and toluene to provide 36.2 g of dl-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride. M. P. 195°-197.5° C.

EXAMPLE 4

Resolution of dl-1-methyl-3-(4-benzyloxyphenyl)-propylamine to provide R-(-)-1-methyl-3-(4-benzyloxy-phenyl)propylamine

A solution of 629.3 g of dl-1-methyl-3-(4-benzyloxy-phenyl)propylaminium chloride was converted to the free amine by reaction with 95 g of sodium hydroxide in 400 ml of water. The free amine was then dissolved in 2000 ml of methylene chloride and added to a solution of 328 g of D-(-)-mandelic acid in 1000 ml of methanol. The mandelic acid salt of the free amine precipitated out of solution and was recrystallized three times from methanol to provide 322 g of the R-mandelic acid salt of R-1-methyl-3-(4-benzyloxyphenyl)propylamine. M. P. 166°-167° C. $[\alpha]_D$−30°, $[\alpha]_{365}$ −119° (MeOH).

The salt so formed was converted to R-1-methyl-3-(4-benzyloxyphenyl)propylamine as the free base by reaction with aqueous sodium hydroxide.

EXAMPLE 5

R,R-N-[2-(4-Benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine

A solution of 93.9 g of R-1-methyl-3-(4-benzyloxy-phenyl)propylamine in 500 ml of N,N-dimethylformamide containing 63.0 g of 1-hydroxybenzotriazole and 104.6 g of R-2-(4-benzyloxyphenyl)-2-hydroxyacetic acid was cooled to 0° C and stirred while a solution of 83.6 g of N,N'-dicyclohexylcarbodiimide in 300 ml of dimethylformamide was added dropwise over one hour. The reaction mixture was stirred for twelve hours at 3° C and then was diluted with 10 ml of water, stirred for an additional hour, and then cooled to −30° C. in an ice-acetone bath. The reaction mixture was filtered to remove dicyclohexylurea, and then the filtrate was concentrated by evaporation of the solvent under reduced pressure. The concentrated solution was diluted with ethyl acetate and washed with saturated aqueous sodium carbonate solution, with water, with 300 ml of 1N hydrochloric acid, and again with water. The organic layer was dried and the solvent was removed by evaporation under reduced pressure to provide the product as a white solid. The solid was recrystallized

once from acetonitrile and again from methanol to provide 159.7 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)-propylamine. M. P. 145°–148° C. $[\alpha]_D - 15.9°$, $[\alpha]_{365} - 50.1°$ (MeOH).

Analysis calc for $C_{32}H_{33}NO_4$: Theory: C, 77.55; H, 6.71; N, 2.83; Found : C, 77.04; H, 6.84; N, 2.53.

EXAMPLE 6

R,R-N-[2-(4-Benzyloxyphenyl)-2-hydroxyethyl]-1-methyl3-(4-benzyloxyphenyl)propylamine

To a stirred solution of 10.0 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine in 500 ml of freshly distilled tetrahydrofuran under a nitrogen gas atmosphere was added dropwise over thirty minutes 41 ml of 2 molar borane-dimethyl sulfide complex in tetrahydrofuran. The reaction mixture was stirred at 25° C. for twenty hours, and then was heated to reflux and stirred for an additional three hours. After cooling the reaction mixture to 25° C. for another eighteen hours, the excess borane was decomposed by the slow portion-wise addition of 400 ml of methanol. The solvent was then removed from the reaction mixture by evaporation under reduced pressure to provide the product as an oil. The oil so formed was dissolved in 250 ml of hot methanol, and after concentrating the volume to 125 ml, the product began crystallizing out of solution. The crystalline product was collected by filtration and recrystallized twice from methanol to provide 6.65 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine. M. P. 119°–123.5° C.

The amine so formed was dissolved in methanol and added to a solution of ethereal hydrogen chloride, thereby providing 6.49 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)-propylaminium chloride. M. P. 214.5°–216° C. $[\alpha]_D - 13.4°$, $[\alpha]_{365} - 30.2°$ (MeOH).

Analysis calc. for $C_{32}H_{36}NO_3Cl$: Theory: C, 74.19; H, 7.00; N, 2.70; Cl, 6.84; Found: C, 74.20; H, 6.98; N, 2.65; Cl, 6.63.

EXAMPLE 7

R,R-1-(4-Hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride, also named as R,R-N-[2-(4-Hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)propylaminium chloride

A mixture of 51.6 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride and 5.0 g of Raney nickel in 2 liters of ethanol and 2 liters of ethyl acetate was stirred at 25° C. for four and one-half hours under a hydrogen atmosphere of 60 psi. The reaction mixture was then filtered to remove the residual Raney nickel, and the filtrate was concentrated to an oil by evaporation of the solvent under reduced pressure, and the oil was crystallized from fresh ethanol and diethyl ether to provide 29.8 g of R,R-N-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)-propylaminium chloride. M. P. 176°–176.5° C. (dec.) $[\alpha]_D - 22.7°$, $[\alpha]_{365} - 71.2°$ (3.7 mg/ml MeOH).

Analysis calc. for $C_{18}H_{24}NO_3Cl$: Theory: C, 63.99; H, 7.16; N, 4.15; Found C, 63.70; H, 7.26; N, 4.32.

EXAMPLE 8

As pointed out above, a preferred embodiment of this invention employs a mixture of all four optical isomers of the compound of Example 7. This racemic mixture can be prepared by the method described above by reaction of dl-4-(benzoyloxy)mandelic acid with dl1-methyl-3-(4-benzyloxyphenyl)propylamine in the presence of DCC to give racemic 1-(4-benzyloxyphenyl)-2-oxo-2-[1-methyl-3-(4-benzyloxyphenyl)propylamino]-ethanol. Reduction of the latter compound and subsequent removal of the benzyl groups provides racemic 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]-ethanol. This compound is more preferably prepared by the following procedure.

A solution of 32.8 g. (0.2 m) of methyl 2-(4-hydroxyphenyl)ethyl ketone and 42.6 g. (0.2 m) of 1-(4-hydroxyphenyl)-2-aminoethanol in 380 ml. of ethanol containing 3.8 g. of five percent palladium on carbon was stirred for sixteen hours at 60° C. under hydrogen at 55 psi. The reaction mixture was then filtered, and the filtrate was diluted by addition of 50 ml. of water. The aqueous mixture was concentrated to a volume of about 400 ml., and then washed with dichloromethane. The aqueous mixture was acidified by addition of 50 ml. of conc. hydrochloric acid. After standing at room temperature for two hours, the aqueous acid mixture was filtered and the filter cake was washed with 40 ml. of ice water and dried at 50° C. in vacuum to provide 47 g. of 1-(4-hydroxyphenyl-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride. M. P. 124°–129° C.

Analysis calc. for $C_{18}H_{24}NO_3Cl$: Theory: C, 63.99; H, 7.16; N, 4.15; Cl, 10.49. Found: C, 63.77; H, 6.80; N, 3.91; Cl, 10.68.

^3C NMR studies demonstrated the product to be comprised of 51% RR,SS diastereamer and 49% RS,SR diastereomer.

EXAMPLE 9

1-Phenyl-2-[1-methyl-3-(4-nitrophenyl)-propylamino]ethanol

A solution of 5.0 g. (25.9 mM) of 2-amino-1-phenylethanol and 3.55 g. (25.9 mM) of methyl 2-(4-nitrophenyl)ethyl ketone in 60 ml. of toluene containing 10 mg. of para-toluenesulfonic acid was heated at reflux for six hours in a flask equipped with a Dean-Stark trap. The water that formed during the reaction was removed via the trap, and then the reaction mixture was cooled to room temperature and concentrated to dryness by evaporation of the solvent under reduced pressure. The solid product that remained was dissolved in 50 ml. of tetrahydrofuran and the solution was heated to reflux. A solution of 3.5 ml. of 2N borane-methyl sulfide complex in tetrahydrofuran was then added dropwise to the reaction mixture, and the mixture was refluxed for an additional ninety minutes. After cooling the reaction mixture to room temperature, it was diluted by addition of diethyl ether saturated with hydrogen chloride. The precipitate that formed was collected by filtration and crystallized from ethanol and diethyl ether to give 3.29 g. of 1-phenyl-2-[1-methyl-3-(4-nitrophenyl)-propylamino]ethanol hydrochloride. M. P. 203-213° C.

Analysis calc. for $C_{18}H_{23}ClN_2O_3$: Theory: C, 61.62; H, 6.61; N, 7.98; Cl, 10.1. Found: C, 61.76; H, 6.62; N, 7.76; Cl, 10.13.

EXAMPLE 10

1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]ethanol

A solution of 32.6 g. (0.2 m) of 1,1-dimethyl-3-phenylpropylamine and 22.9 g. (0.1 m) of 2-(4-methoxyphenyl)-2-oxoethyl bromide in 75 ml. of tetrahydrofuran was heated at reflux for thirty-six hours. The reaction mixture was then cooled and added to 2 liters of diethyl ether. The precipitate was removed by filtration, and the filtrate was acidified with hydrobromic acid to give 18.15 g. of 1-(4-methoxyphenyl)-1-oxo-2-(1,1-dimethyl-3-phenylpropylamino)ethane hydrobromide. M. P. 174°–178° C.

The compound thus formed was dissolved in 85 ml. of glacial acetic acid containing 35 ml. of hydrobromic acid, and the solution was heated at reflux for nine hours. The solution was then cooled and the solvent was removed by evaporation to provide, following crystallization from ethanol and diethyl ether, 7.8 g. of 1-(4-hydroxyphenyl)-1-oxo-2-(1,1-dimethyl-3-phenylpropylamino) ethane hydrobromide. M. P. 228°–230° C.

Catalytic hydrogenation of 5.0 g. of the compound from above in 44 ml. of ethanol containing 1.25 g. of five percent palladium on carbon afforded, following crystallization from acetone and diethyl ether, 2.3 g. of 1-(4-hydroxyphenyl)-2-(1,1-dimethyl3-phenylpropylamino)ethanol hydrobromide. M. P. 168°–170° C.

Analysis calc. for $C_{19}H_{26}BrNO_2$: Theory: C, 60.00; H, 6.89; N, 3.68. Found: C, 60.28; H, 6.67; N, 3.62.

EXAMPLE 11

1-(3-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethanol

To a stirred solution of 67.2 g. (0.22 M) of 2-(3-benzyloxyphenyl)-2-oxoethyl bromide in 200 ml. of acetonitrile was added a solution of 54.3 g. (0.20 M) of N-benzyl-1,1-dimethyl-3-(4-fluorophenyl)propylamine in 600 ml. of acetonitrile containing 42 ml. (0.22 M) of diisopropylethylamine. The reaction mixture was stirred for about six hours at reflux, and then was cooled and stored at room temperature for forty-eight hours. The reaction mixture was next diluted by addition of aqueous sodium hydroxide, and the organic solvents were removed by evaporation under reduced pressure. The aqueous alkaline mixture was extracted with ethyl acetate, which was then washed with water, dried, and concentrated to dryness to give an oil. The oil was dissolved in ethanol and diethyl ether and converted to the hydrochloride salt by addition of excess hydrogen chloride. The precipitated solid was collected by filtration and recrystallized from ethyl acetate to give 51.3 g. of 1-(3-benzyloxyphenyl)1-oxo-2-[(N-benzyl)-1,1-dimethyl-3-(4-fluorophenyl)-propylamino]ethane hydrochloride. M. P. 137°–145° C.

The compound thus prepared was reduced by reaction with 16 g. of sodium borohydride in ethanol. Isolation of the product, followed by conversion to the hydrochloride salt and crystallization from diethyl ether afforded 55.0 g. of 1-(3-benzyloxyphenyl)-2-[(N-benzyl)-1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethanol hydrochloride. M. P. 186.5°–191° C.

A solution of 10.0 g. of the product thus produced in 200 ml. of ethanol containing 3.0 g. of Raney Nickel was shaken for two hours at 25° C. under hydrogen at 44 psi. The reaction mixture was then filtered, and the solvent was removed from the filtrate by evaporation under reduced pressure to give a white solid. The solid was triturated with ethyl acetate and air dried to provide 5.9 g. of 1-(3-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethanol hydrochloride. M. P. 196.5°–198.5° C.

Analysis calc. for $C_{19}H_{25}ClFNO_2$: Theory: C, 64.49; H, 7.12; N, 3.96; Cl, 10.02. Found: C, 64.29; H, 6.97; N, 4.06; Cl, 9.89.

EXAMPLE 12

1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamine]ethanol

A suspension of 10.0 g. (50 mM) of 1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamine and 15.0 g. (50 mM) of 1-(4-benzyloxyphenyl)-1-oxoethyl bromide in 1000 ml. of acetonitrile containing 32.0 g. (0.3 M) of sodium carbonate and 100 ml. of water was stirred for one hour at 25° C. The precipitate that formed was collected by filtration, washed with water and with diethyl ether, and air dried to provide 8.0 g. of 1-(4-benzyloxyphenyl)-1-oxo-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)-propylamino]ethane. M. P. 184°–187° C. This product was converted to the hydrochloride salt by reaction with hydrogen chloride in diethyl ether. M. P. 219°–224° C.

The compound thus prepared was reacted with sodium borohydride in methanol to provide, following conversion to the hydrochloride salt and crystallization from methanol and diethyl ether, 5.8 g. of 1-(4-benzyloxyphenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride. M. P. 141°–143° C.

Reaction of the above compound with hydrogen in the presence of Raney Nickel effected cleavage of the hydroxy protecting group to afford, following crystallization of the hydrochloride salt, 1.3 g. of 1-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride. M. P. 185° C. (dec.)

Analysis calc. for $C_{20}H_{27}ClN_2O_3$: Theory: C, 63.40; H, 7.18; N, 7.39; Cl, 9.36. Found: C, 63.26; H,.7.01; N, 7.45; Cl, 9.42.

The compounds of Examples 13 and 14 were prepared by the general procedure of Example 12.

EXAMPLE 13

1-(2-Fluorophenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride

M. P. 227°–230° C.

EXAMPLE 14

1-(3-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrobromide

M. P. 161°–165° C.

EXAMPLE 15

1-Phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl)-propylamino]ethanol hydrochloride

Methyl 2-(4-methylthiophenyl)ethyl ketone was oxidized by reaction with m-chloroperbenzoic acid to give methyl 2-(4-methylsulfonylphenyl)ethyl ketone. A solution of 6.73 g. of 2-amino-1-phenylethanol and 11.10 g. of methyl 2-(4-methylsulfonylphenyl)ethyl ketone in 500 ml. of toluene containing 200 mg. of -toluenesulfonic acid was heated at reflux for twenty-four hours. The reaction mixture was cooled and the solvent was removed by evaporation to give the Schiff base 1-phe-

nyl-2-[1-methyl-3-(4-methylsulfonylphenyl)-propylimino]ethanol. The Schiff base thus prepared was reacted with 3.7 g. of sodium borohydride in 500 ml. of ethanol at 0° C. for sixteen hours. The reaction mixture was diluted by addition of 50 ml. of acetone and 20 ml. of 3N hydrochloric acid. The mixture was concentrated to an oil by evaporation of the solvent. The oil crystallized upon standing at room temperature. Recrystallization of the product from 200 ml. of hot ethanol afforded 8.96 g. (48% yield) of 1-phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl)propylamino]ethanol hydrochloride. M. P. 164°–170° C.

Analysis calc. for $C_{19}H_{26}ClNO_3S$: Theory: C, 59.44; H, 6.83; N, 3.65; Cl, 9.23; S, 8.35. Found: C, 59.28; H, 6.57; N, 3.70; Cl, 9.36; S, 8.11.

EXAMPLE 16

Premix for Chickens

Premix for Chickens

Ingredient	% by weight
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]-ethanol succinate	25
Ground Corn	74
Sodium Chloride	1
	100

EXAMPLE 17

Premix for ruminants

Premix for ruminants

Ingredient	% by weight
1-(2-fluorophenyl)-2-[1,1-dimethyl-3-(4-aminocarbonyl-phenyl)propylamino]ethanol	30
Ground yellow corn	60
Alfalfa meal	10
	100

EXAMPLE 18

Premix for Swine

Premix for Swine

Ingredient	% by weight
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol hydrochloride	10
Soybean mill run	88
Mineral oil	2
	100

The above ingredients are blended to uniformity to provide a dry flowable premix that can be admixed with a typical animal feed ration at a rate to provide about 20 ppm of active ingredient in the final feed ration. For example, the premix can be added to the following swine grower ration for convenient oral administration of the β-phenethanolamine to swine.

Ingredient	% by weight	lbs/Ton
Corn, yellow, ground	76.70	1534
Soybean Oil Meal, solvent extracted, dehulled	19.35	387
Calcium Carbonate	1.20	24
Dicalcium Phosphate, feed grade	1.20	24
Salt (sodium chloride)	0.50	10
Trace mineral premix, AN-03[1]	0.10	2
Swine Vitamin Premix, SW-03[2]	0.65	13
Vitamin A Premix, 3M USP units/lb.[3]	0.05	1
Methionine Hydroxy Analogue, 93%	0.20	4
Selenium Premix[4]	0.005	1
	100.00	2000

[1]Each Kg of premix contains: 50 g. manganese as manganese sulfate; 100 g. zinc as zinc carbonate; 50 g. iron as ferrous sulfate; 5 g. copper as copper oxide; 1.5 g. iodine as potassium iodide and 150 g. maximum and 130 g. minimum calcium as calcium carbonate.

[2]Each Kg of premix contains: 77,161 IU Vitamin D_3; 2,205 IU Vitamin E; 411 mg. riboflavin; 1,620 mg. pantothenic acid; 2,205 mg. niacin; 4.4 mg. Vitamin B_{12}; 441 mg. Vitamin K; 19,180 mg. choline; 110 mg. folic acid; 165 mg. pyridoxine; 110 mg. thiamine; 22 mg. biotin.

[3]Each Kg of premix contains 6,613,800 IU Vitamin A.

[4]Each Kg of premix contains 200 mg. of selenium as sodium selenite.

EXAMPLE 19

Feed Ration for Lambs

Feed Ration for Lambs

Ingredient	Percent	lbs/T
Yellow corn	61.00	1220.0
Corn cobs	20.00	400.0
Alfalfa Meal, dehydrated	5.40	108.0
Soybean oil meal	8.00	160.0
Urea, feed grade	0.50	10.0
Molasses, cane	3.00	60.0
Dicalcium phosphate	0.43	8.6
Salt	0.30	6.0
Calcium carbonate	0.14	2.3
Trace mineral premix[1]	0.03	0.6
Vitamin A + D_3 Premix[2]	0.10	2.0
Vitamin E Premix[3]	0.10	2.0
1-(4-Hydroxyphenyl)-2-(1,1-dimethyl-3-phenylpropylamino)-ethanol	1.00	20.0
	100.00	2000.0

[1]Trace mineral premix contains: 2.5% manganese as manganese oxide, 0.07% iodine as potassium iodide, 0.3% cobalt as cobalt carbonate, 0.5% copper as copper oxide, and 20.0% zinc as zinc sulfate.

[2]Each pound of vitamin A and D_3 premix contains 2,000,000 USP units Vitamin A and 225,750 USP units Vitamin D_3.

[3]Each pound of Vitamin E premix contains 20,000 IU Vitamin E.

The compounds to be employed in the method of this invention have demonstrated efficacy in animal tests designed to establish beneficial nutritional effects. In one test designed to show lipolytic activity, normal swine, either barrows or gilts, were employed to analyze the effect of compounds on blood glucose, insulin, and non-esterified fatty acids (NEFA).

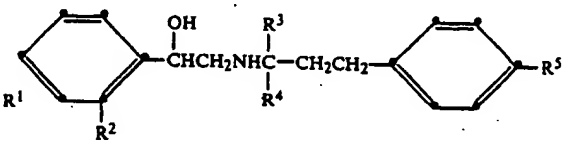
Test animals were maintained in metabolism crates, and following a period of adaptation, catheters were placed in their femoral veins. Prior to administration of the test compounds, all animals were fasted for a period of forty hours. Such fasting causes an elevation of NEFA's in the blood. On the day of the test, all animals were fed a normal feed ration, and one group of animals were held as controls while another group of animals received a test compound. The test compounds were administered at 200 mcg/kg intravenously, or orally at 1 mg/kg. Blood samples were taken from each animal immediately prior to treatment and then at one hour intervals for a period of six hours following treatment. The blood plasma was analyzed for glucose, insulin and NEFA content.

When the fasted pigs were fed the normal feed ration without a test compound, the NEFA levels in the blood drop dramatically and remained low. A β-phenethanolamine as defined herein caused either an elevation in NEFA's, or inhibited the drop in NEFA's. Blood levels of glucose and insulin were also elevated with the β-phenethanolamines.

The following Table presents the lipolytic activity of several preferred β-phenethanolamines when evaluated according to the test described above. The results are averages of several tests.

TABLE I

Lipolytic Activity (increase in NEFA's)



R^1	R^2	R^3	R^4	R^5	% increase in NEFA's over control	% increase in glucose over control
H	H	H	CH_3	SO_2CH_3	131	9
p-OH	H	CH_3	CH_3	H	445	48
m-OH	H	CH_3	CH_3	H	71	31
m-OH	H	CH_3	CH_3	F	28	72
p-OH	H	CH_3	CH_3	OH	141	35
p-OH	H	CH_3	CH_3	$CONH_2$	18	169
m-OH	H	CH_3	CH_3	OH	68	40
H	H	H	H	NO_2	199	7
p-OCH_3	H	CH_3	CH_3	H	84	25
p-OCH_3	H	CH_3	CH_3	OH	249	5
H	H	H	CH_3	NO_2	1458	27

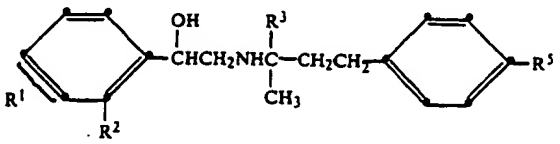
A ten day in vivo study was employed to determine the effect of β-phenethanolamines on feed efficiency and rate of growth. In these studies, barrows and gilts weighing approximately 60 kg were maintained in individual pens. Each treatment was replicated six times in randomly assigned animals, with each test animal forming an experimental unit. A group of control animals received a normal swine grower feed ration comprising the following ingredients:

Ingredient	% by weight
Ground yellow corn	76.70
Soybean oil meal	19.35
Calcium carbonate	1.20
Dicalcium phosphate	1.20
Salt	0.50
Trace mineral premix	0.10
Swine Vitamin premix	0.65
Vitamin A premix, 3M USP units/lb.	0.05
Methionine Hydroxy analogue, 93%	0.20
Selenium premix	0.05
	100.00

The test animals received the same feed ration plus the test compound. All animals received feed and water ad libitum. All animals were weighed on day 1 and again on day 10, and feed consumption was measured by recording all feed issued and any remaining feed on day 10. The results of two series of this 10 day test for several β-phenethanolamines are given in Table II. In the Table, the column labelled "ADG" is the average daily weight gain in pounds; "ADF" is the average daily weight gain in pounds; "ADF" is the average daily feed consumption (in pounds) by the test animals; and F/G is the feed efficiency calculated as ADF divided by ADG.

TABLE II

Growth Promotion and Feed Efficiency



	R^1	R^2	R^3	R^5	dose ppm	ADG	ADF	F/G
Experiment I	Control					1.60	4.7	2.98
	p-OH	H	H	OH	20	2.19	5.0	2.33
	H	H	H	NO_2	20	1.78	4.22	2.37
Experiment II	Control					1.34	4.16	3.22
	p-OH	H	CH_3	H	20	1.60	4.26	2.66
	m-OH	H	CH_3	F	20	1.52	4.57	3.01

The β-phenethanolamines to be employed in the method of this invention can be administered in combination with other compounds known to have a beneficial effect upon animals. Typical compounds to be coadministered with the β-phenethanolamines include antibiotics, for example any of the tetracyclines, tylosin, penicillins, cephalosporins, polyether antibiotics, glycopeptides, orthosomycins and related compounds commonly administered to swine, poultry, ruminants and the like. A preferred combination to be employed in the present method is an antibiotic such as tylosin or a tetracycline, together with 1(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol. Such combinations will comprise the respective components in a ratio of about 1 to about 2 parts by weight of β-phenethanolamine and about 1 to about 10 parts by weight of the partner component.

In a typical treatment, 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol was evaluated in a 42-day study employing finishing swine. Each treatment was replicated four times, with three pigs per replication. All treatments included a normal feed diet plus tylosin at 40 g/T. The animals were tested for growth performance and feed efficiency enhancement. Carcass quality was determined by analysis for fat and muscling. The results of the study are given in

Table III. Both β-phenethanolamine treatments resulted in improved growth performance and carcasses with less fat and more muscle.

TABLE III

Growth Promotion, Feed Efficiency and Carcass Quality					
	β-phenethanolamine[2]				
	Control[1]	20 g/T	% change	40 g/T	% change
ADG	1.94	2.07	(6.7)	2.05	(5.7)
ADF	6.28	6.63	(5.6)	6.64	(5.7)
F/G	3.24	3.20	(−1.2)	3.24	(0)
Live Wt. at Slaughter, lb	217.0	223.0	(2.8)	221.0	(1.8)
Chilled Carcass Wt., lb	154.6	160.5	(3.8)	159.8	(3.4)
Fat Depth at 10th Rib, in	1.15	1.09	(−5.2)	1.05	(−8.7)
Loin Eye Area Sp., in	4.64	4.91	(5.8)	4.84	(4.3)
Estimated pounds of Fat Free Muscle[3]	74.2	78.8	(6.1)	78.4	(5.7)

[1]all diets contained 40 g/T of tylosin
[2]1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol hydrochloride
[3]A regression equation was employed in arriving at the numerical predictions of carcass muscle (J. Animal Science, 1977, Vol. 44:8-17).

The data reported in Table III further demonstrates that the β-phenethanolamines described herein promote growth, improve feed efficiency improve leaness.

In a similar study conducted over a 61 day period, a group of control animals received a normal daily feed ration with no additive. Another group of animals received the feed ration plus tylosin at 40 g/T, while another group received the feed ration plus 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride (compound A) at 20 g/T. A final group of finishing swine received the feed ration plus the combination of 40 g/T of tylosin and 20 g/T of the phenethanolamine. The results of this trial are given in Table IV.

TABLE IV

	Control	Tylosin	A	Tylosin + A
ADG	1.63	1.64	1.36	1.50
ADF	5.64	5.77	5.10	5.38
F/G	3.46	3.51	3.77	3.59
Slaughter Wt. (lbs)	210	211	193	201
Carcass Wt. (lbs)	150.3	151.5	140.1	146.3
Fat Depth, 10th rib, (in)[1]	0.96	0.96	0.80	0.85
Loin Eye Area (in^2)[1]	4.60	4.68	4.92	5.00
Est. % Muscle[2]	49.2	49.2	51.4	51.2
Est. Pounds Muscle[2]	75.3	76.5	74.1	76.8

[1]These results are based upon measurement of fat at the 10th rib after the carcass is split in half across the backbone.
[2]A regression equation is employed in arriving at the numerical predictions of carcass muscle (J. Animal Science, 1977, Vol. 44:8-17).

As in the previous study, both phenethanolamine treatments resulted in carcasses with less fat and more muscle. It should also be noted that the estimated amount of carcass muscle produced with the Tylosin + A treatment was similar to that produced in the control and the Tylosin treatment alone. This result was achieved, however, with less feed consumption than either the control or the Tylosin treatments.

Additional studies have been carried out to demonstrate the anabolic effect of β-phenethanolamines in swine. The effect of the compounds on nitrogen retention is the difference between nitrogen intake and nitrogen excreted. Increased nitrogen retention is known to be associated with increased anabolic activity, resulting in improved carcass muscling and leanness.

In a typical study, barrows weighing about 172 pounds (78 Kg) were orally administered various doses of 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride (Compound A). All animals received water and a constant amount of normal swine feed ration. The results of this study are presented in Table V, and show that all β-phenethanolamine treatments improved nitrogen retention compared to controls.

TABLE V

Treatment	Nitrogen Retention Animals per treatment	Nitrogen Retained (g/day)
Control	6	21.0
Compound A (5 g/T)	3	23.6
Compound A (10 g/T)	3	23.9
Compound A (20 g/T)	3	25.0

As pointed out above, the method of this invention can be practiced with individual isomers of β-phenethanolamines or with mixtures of isomers and diastereomers. In a study to determine the effect on weight gain and feed efficacy of various mixtures of diastereomers, barrows initially weighing about 177 pounds were fed a normal swine diet plus a β-phenethanolamine at 20 g/T of feedstuff. Each treatment was replicated in twelve individually fed animals. The results were presented in Table VI and show that growth performance was improved by both β-phenethanolamine treatments with very little change in feed intake.

TABLE VI

Treatment	Average Daily Feed (lbs)	Average Daily Gain (lbs)
Control	5.89	1.58
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride 57.5% RR,SS 42.5% RS,SR	5.94	2.15
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride 47% RR,SS 53% RS,SR	5.86	1.95

The data in Table VI demonstrates that the method of improving feed efficiency and promoting growth can be practiced with any desired mixture of β-phenethanolamine optical isomers.

The efficacy of the β-phenethanolamines described herein also has been demonstrated in poultry. In a typical study, broilers that were twenty-one days old were administered an oral dosing of a β-phenethanolamine in their normal daily feed ration. All animals received the following broiler finisher ration:

Ingredients	% by weight	lbs/T
Ground yellow corn	66.40	1328.00
Animal-vegetable fat	1.53	30.60
Corn Glut. meal (60%)	4.00	80.00
Soybean meal (48%)	19.19	383.80
Fish meal-menhaden	2.50	50.00
Dicalcium phosphate	1.01	34.20
Feather meal-Hydr.	2.50	50.00
Ground limestone	0.83	16.60
Salt	0.30	6.00

-continued

Ingredients	% by weight	lbs/T
Vitamin Premix[1]	0.50	10.00
Trace mineral premix[2]	0.10	2.00
Methionine Hyd. Anal.	0.15	3.00
Lysine HCl	0.29	5.80
	100.00	2000.00

[1]Vitamin premix provides 3000 IU of vitamin A, 900 ICU of vitamin D_3, 40 mg. of vitamin E, 0.7 mg. of vitamin K, 1000 mg of choline, 70 mg. of niacin, 4 mg of pantothenic acid, 4 mg of riboflavin, 100 mcg of vitamin B_{12}, 100 mcg of biotin and 125 mg of ethoxyquin per kg of complete feed.
[2]Trace mineral premix provides 75 mg of manganese, 50 mg of zinc, 25 mg of iron and 1 mg of iodine per kg of complete feed.

Test animals received with the above ration varying doses of 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride (compound A). Each treatment was replicated sixteen times, and the test was terminated when the animals reached fifty-six days of age. The animals were analyzed for weight gain and feed efficiency. The results of this test in broilers is presented in Table VII as mean weight gain and mean feed to gain ratios.

TABLE VII

		Growth Performance of Broilers			
				Feed Efficiency	
		Weight Gain		Feed/	% change
Treatment	Dose (g/T)	grams	% improvement	Gain Ratio	from control
Control		1473	0	2.336	0
Compound A	10	1585	7.6	2.292	1.9
Compound A	20	1613	9.5	2.298	1.6
Compound A	40	1550	5.2	2.312	1.0
Compound A	80	1669	13.3	2.221	4.9

The results of this study demonstrate that the β-phenethanolamines described herein are effective in promoting growth and improving feed efficiency in poultry.

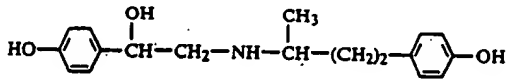
The compounds of the invention also have demonstrated efficacy in ruminants. Forth-eight crossbred wether lambs were employed in a test designed to show the effects of Compound A (1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride) at varying doses. Sixteen animals were held as controls, while sixteen received 40 ppm of Compound A, and another sixteen received 80 ppm of Compound A. All animals received a normal daily feed ration and water ad libitum. Average daily weight gain and average daily feed consumption after twenty-eight days is given below in Table VIII. The data demonstrates that a β-phenethanolamine as defined herein is effective in promoting growth and improving feed efficiency in ruminants.

TABLE VIII

		Growth Performance of Lambs		
Treatment	Dose (ppm)	ADG (lbs)	ADF (lbs)	F/G
Control	0	0.414	3.68	8.89
Compound A	40	0.418	3.61	8.64
Compound A	80	0.472	3.57	7.56

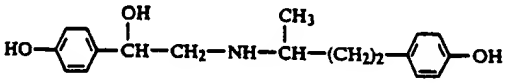
We claim:

1. A method for promoting the growth of poultry comprising administering to a the poultry a growth promoting amount of a compound of the formula



or an acid addition salt thereof.

2. A method for improving the efficiency of feed utilization by poultry comprising administering to a the poultry an effective amount of a compound of the formula



or an acid addition salt thereof.

3. The method of claim 1 employing 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride.

4. The method of claim 1 employing R,R-1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol, or an acid addition salt thereof.

5. The method of claim 2 employing 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride.

6. The method of claim 2 employing R,R-1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol, or an acid addition salt thereof.

7. The method of claim 1 wherein the fowl is a chicken.

8. The method of claim 1 wherein the fowl is a turkey.

* * * * *

Exhibit XIV

U.S. Patent 5,643,967

US005643967A

United States Patent [19]

Anderson et al.

[11] Patent Number: 5,643,967

[45] Date of Patent: Jul. 1, 1997

[54] **GROWTH PROMOTION**

[75] Inventors: **David B. Anderson**, Greenfield; **Klaus K. Schmiegel**, Indianapolis; **Edward L. Veenhuizen**, Greenfield, all of Ind.; **Ronald R. Tuttle**, Escondido, Calif.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[21] Appl. No.: **37,789**

[22] Filed: **Mar. 18, 1993**

Related U.S. Application Data

[60] Continuation of Ser. No. 606,670, Oct. 31, 1990, abandoned, which is a division of Ser. No. 328,996, Mar. 27, 1989, Pat. No. 4,992,473, which is a division of Ser. No. 153,640, Feb. 8, 1988, Pat. No. 4,849,453, which is a division of Ser. No. 860,719, May 7, 1986, Pat. No. 4,734,437, which is a continuation of Ser. No. 628,002, Jul. 5, 1984, abandoned, which is a continuation of Ser. No. 462,587, Jan. 31, 1983, abandoned.

[51] **Int. Cl.**[6] **A61K 31/135**

[52] **U.S. Cl.** **514/653**

[58] **Field of Search** 514/653

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,818,101	6/1974	Baile et al.	514/653
4,992,473	2/1991	Anderson et al.	514/653

FOREIGN PATENT DOCUMENTS

0049728	4/1982	European Pat. Off. .
2028801	3/1980	United Kingdom .

OTHER PUBLICATIONS

Fed Proc. 42 #3 (1983).
Fed Proc 42 #4 (1983).

Primary Examiner—Kevin E. Weddington
Attorney, Agent, or Firm—Paul R. Cantrell; Kathleen R. S. Page; David E. Boone

[57] **ABSTRACT**

β-Phenethanolamines are effective in promoting growth and improving feed efficiency and leanness in animals.

38 Claims, No Drawings

GROWTH PROMOTION

This application is a continuation of application Ser. No. 07/606,670, filed Oct. 31, 1990, now abandoned which was a division of Ser. No. 07/328,996, filed Mar. 27, 1989, U.S. Pat. No. 4,992,473 which was a division of Ser. No. 07/153,640, filed Feb. 8, 1988, U.S. Pat. No. 4,849,453, which was a division of Ser. No. 06/860,719, filed May 7, 1986, U.S. Pat. No. 4,734,437, which was a continuation of Ser. No. 06/628,002, filed Jul. 5, 1984, now abandoned, which was a continuation of Ser. No. 06/462,587, filed Jan. 31, 1983, now abandoned.

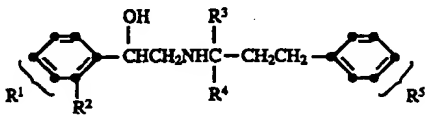
BACKGROUND OF THE INVENTION

The chemistry and use of β-phenethanolamines has been extensively investigated. A number of these compounds have been reported to have beneficial cardiac activities; see U.S. Pat. No. 3,987,200. Such compounds also are known to have sympathomimetic activity, and have found utility as utero-relaxing agents; Van Dijk et al., *Recueil*, 92, 1281 (1973). More recently, a group of β-phenethanolamines have been reported as possessing anti-hyperglycemic activity, and have been found effective in promoting the loss of weight in animals, EPO 6735 published Jan. 9, 1980.

An object of this invention is to provide a new use for certain β-phenethanolamines. This invention provides a method for promoting the growth of domesticated animals employing β-phenethanolamines.

SUMMARY OF THE INVENTION

This invention provides a method for increasing weight gain in animals and improving the efficiency of feed utilization and the quality of the carcass. The invention is more particularly directed to a method for promoting growth and improving feed efficiency and leanness comprising administering an effective amount of a compound having the formula



wherein:

R^1 is hydrogen, hydroxy, or methoxy;

R^2 is hydrogen or fluoro,

R^3 is hydrogen or C_1–C_2 alkyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, fluoro, nitro, hydroxy, SO_2CH_3 or $CONH_2$; provided that R^1 is hydrogen only when R^5 is nitro or SO_2CH_3; and the acid addition salts thereof.

A preferred method for promoting growth and improving feed efficency and leanness according to this invention employs a compound of the above formula wherein R^1 is hydroxy, R^2 is hydrogen, R^3 is hydrogen or methyl and R^4 is methyl. The method is most preferably practiced employing a compound wherein R^1 and R^5 both are hydroxy and R^2 and R^3 both are hydrogen and R^4 is methyl. When R^1 is hydroxy or methoxy, it preferably is in the para position. When R^5 is other than hydrogen, it also is preferably in the para position.

This invention also provides an animal feedstuff comprising a β-phenethanolamine of the above formula together with a suitable carrier therefor.

DETAILED DESCRIPTION OF THE INVENTION

The compounds employed in the method provided by this invention are either known in the art or are readily prepared by well known synthetic procedures. A particularly preferred method employs 1-(3-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol. This β-phenethanolamine is disclosed in South African Patent No. 673,994 published in May, 1967. The most preferred embodiment of this invention employs 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol, a compound disclosed as having utero-relaxing, activity by Van Dijk et al. in *Recueil*, 92 1281 (1973).

The compounds to be employed in the method of this invention are readily prepared by reaction of a styrene oxide with a 3-phenylpropylamine derivative. For example, a styrene oxide such as 2-fluorostyrene oxide can be reacted with about an equimolar quantity of an amine such as 1-methyl-3-(4-nitrophenyl)propylamine in an unreactive organic solvent such as ethanol, methanol, n-propanol, dioxane, or the like. The reaction generally is carried out at a temperature of about 50° to about 120° C., and at such temperature the reaction routinely is substantially complete within about 6 to about 10 hours. The product, a β-phenethanolamine, is readily isolated by simply removing the reaction solvent, for instance by evaporation under reduced pressure, and further purification can be accomplished if desired by standard techniques, including crystallization, chromatography, acid-base extraction, and the like.

An alternative method for preparing the β-phenethanolamines to be employed in the present method comprises reacting a mandelic acid derivative with a 3-phenylpropylamine derivative to provide an amide, which upon subsequent reduction provides a compound of the above formula. For example, a phenylpropylamine derivative such as 1-methyl-3-(3-fluorophenyl)propylamine can be reacted with an acylating agent such as a hydroxy protected mandelic acid halide, or preferably simply reacted with a mandelic acid in the presence of a common peptide coupling reagent such as N,N'-dicyclohexylcarbodiimide, carbonyldiimidazole, N-ethoxy-carbonyl-2-ethoxy-1,2-dihydroquinoline, commonly referred to as EEDQ. The direct coupling reaction generally is conducted in an organic solvent such as benzene or N,N'-dimethylformamide, and normally is complete after about 2 to 48 hours when carried out at about −30° to about 100° C. The product is an amide that is readily isolated by simply filtering the reaction mixture and then removing the reaction solvent. The amide thus formed is next reduced by reaction with a common reducing agent such as diborane or the like to provide a β-phenethanolamine defined by the above formula.

A similar, yet alternative, method of synthesis comprises reacting a phenethanolamine with a phenylethyl ketone to provide a Schiff base, which upon reduction gives a compound to be employed in the present method. For example, a phenethanolamine such as 2-hydroxy-2-(4-hydroxyphenyl)ethylamine can be reacted with a ketone such as methyl 2-(4-hydroxyphenyl)ethyl ketone to provide the corresponding imine, which upon reduction, for instance with 5% palladium on carbon, provides 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl) propylamino]ethanol.

It should be noted that the compounds to be employed in the method of this invention possess at least one asymmetric center (i.e. the carbinol center), and when R^3 and R^4 differ,

the compounds possess two asymmetric centers. Since employment of individual optical isomers necessitates preparing the β-phenethanolamines from optically active starting materials, or using costly separation procedures, a preferred embodiment of this invention employs a mixture of optical isomers. For example, 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol is preferably prepared from racemic mixtures of starting materials, e.g. dl-1-methyl-3-(4-hydroxyphenyl)propylamine and dl-4-hydroxystyrene oxide, to provide a mixture of all four possible optical isomers of the product. The mixture of optical isomers is employed in the method without subsequent separation of isomers.

Since the β-phenethanolamines to be employed in the present method are inherently basic, they readily form acid addition salts with any number of inorganic and organic acids. These salts can be employed in the method of the invention, and often are preferred to the free base since they generally are more soluble in solvents such as water and are more conveniently formulated as an animal feedstuff. Acids commonly employed to form acid addition salts include mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid, perchloric acid and the like; and organic acids such as acetic acid, citric acid, succinic acid, para-toluene sulfonic acid, methanesulfonic acid, lactic acid and the like. Preferred salts to be employed in the present method include the hydrochlorides and hydrobromides.

Typical β-phenethanolamines to be employed in the method of this invention include the following:

1-(3-hydroxyphenyl)-2-[1-methyl-1-ethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol;

1-(2-fluoro-4-hydroxyphenyl)-2-[1-methyl-3-(4-fluorophenyl)propylamino]ethanol;

1-(4-hydroxyphenyl)-2-[3-(3-nitrophenyl)propylamino]ethanol;

1-(3-hydroxy-2-fluorophenyl)-2-[3-(4-methylsulfonyl)propylamino]ethanol;

1-(4-methoxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol;

1-phenyl-2-[1,1-dimethyl-3-(3-methylsulfonyl-phenyl)propylamino]ethanol;

1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride;

1-(phenyl)-2-[1-methyl-3-(4-nitrophenyl)-propylamino]ethanol;

1-(3-hydroxyphenyl)-2-[1-methyl-3-(4-fluorophenyl)propylamino]ethanol succinate;

1-(4-hydroxyphenyl)-2-[1-methyl-1-ethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol;

1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]ethanol hydrobromide; and

d-1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol.

The method of promoting growth and improving leanness and feed efficiency provided by this invention is practiced by administering an effective amount of a compound defined above to a warm-blooded animal that receives a nutritionally adequate diet. The method generally will be practiced on domesticated animals raised for human meat consumption, for example grower/finisher swine, poultry, ruminants and the like. In a preferred embodiment, the growth of pigs, chickens and turkeys is promoted employing a β-phenethanolamine. Another preferred embodiment is practiced in ruminants such as cattle, sheep and goats. The method of improving leanness is not limited to meat producing animals, and can be practiced on other warm-blooded animals, including dogs and cats. This latter embodiment is particularly useful when it is desired to maintain mature animals in a relatively lean physical state.

The method of the invention is preferably practiced by orally administering an effective amount of a β-phenethanolamine to an animal. Other routes of administration can be employed, for instance intramuscular or intravenious injection; however, such routes are less practical. The amount to be administered to an animal is an amount that is effective in causing a promotion of growth, or an improvement in the efficiency of utilization of food, or an improvement in carcass quality of the animal, for instance in the form of less fatty tissue and improved leanness. The effective amount to be administered will vary somewhat depending upon the particular animal species being treated and the particular active ingredient employed, but generally will be from about 1 to about 1000 parts per million (ppm) of total daily feed intake. Such amount will provide a dosage of about 0.05 to about 50 mg/kg. A preferred embodiment employs about 1 to about 200 ppm, and more preferably from about 5 to about 100 ppm. A typical amount of active ingredient to be administered to swine will be from about 5 to about 40 ppm. For example, when practicing the method in animals such as ruminants or swine, the compound will be added to the daily feed ration at about 5 to about 100 parts per million of the daily feed ration.

For oral administration, the active β-phenethanolamine is preferably admixed with suitable carriers or diluents commonly employed in animal husbandry. Animal feedstuffs comprising a β-phenethanolamine growth promoter as defined herein are provided as a further embodiment of this invention. Typical carriers and diluents commonly employed in such feedstuffs include corn meal, soybean meal, alfalfa meal, rice hulls, soybean mill run, cottonseed oil meal, bone meal, ground corn, corncob meal, sodium chloride, urea, cane molasses and the like. Such carriers promote a uniform distribution of the active ingredient in the finished feed ration into which such compositions are added, thereby ensuring proper distribution of the active ingredient throughout the feed. The feedstuff composition provided by the invention will contain about 5 to about 95 percent by weight of active ingredient, and more typically about 10 to about 50 percent by weight. As already noted, the acid addition salts of the active phenethanolamines are generally preferred for oral administration, and are thus the preferred form of active ingredient for the feedstuff compositions of the invention.

While the preferred method for orally administering the growth promoters is via the daily feed rations, the compounds can be incorporated into salt blocks and mineral licks, as well as being added directly to drinking water for convenient oral consumption. The compounds can additionally be formulated with polymorphous materials, waxes and the like for long-term controlled release, and administered to an animal as a bolus or tablet only as needed to maintain the desired daily payout of active ingredient.

For parenteral administration, the β-phenethanolamines can be admixed with conventional carriers such as corn oil, sesame oil, carbowax, calcium stearate and the like. Such formulations can be molded into pellets and administered as an injection or as a slow-release subcutaneous implant. Such administrations can be made as often as needed to ensure the proper dosing of active ingredient to obtain the desired rate of growth promotion and improvement in leanness and feed efficiency.

While the compounds described herein are effective in promoting average daily weight gain and improving feed efficiency in animals, they also cause observable improve-

ment in the quality of the meat produced. For example, the compounds appear to mobilize free fatty acids from fatty tissue and depress the deposition of fat as the animals gain weight. This reduction of fat is beneficial since the animal being treated according to the invention gains weight in the form of more useable lean meat, thereby reducing waste and improving the value of the animal thus treated. Also, mature animals that are not subject to additional weight gain can be maintained in a desirably lean form by administering a compound as described herein.

The practice of the present invention is more fully illustrated by the following detailed examples:

EXAMPLE 1

Preparation of d1-4-(benzyloxy)mandelic acid

A solution of 5.0 g of d1-4-hydroxy mandelic acid, 11.0 g of benzyl chloride and 10.0 g of potassium carbonate in 50 ml of methanol was heated to reflux and stirred for seventy-two hours. The reaction mixture was cooled to room temperature and diluted with 50 ml of water. The aqueous solution was washed twice with 50 ml portions of benzene, and then was acidified with concentrated hydrochloric acid. The aqueous acid solution was extracted three times with 50 ml portions of ethyl acetate. The organic extracts were combined, washed with water and with saturated sodium chloride solution and dried. Removal of the solvent by evaporation under reduced pressure provided 5.7 g of a solid which was then recrystallized from 300 ml of toluene to afford 5.33 g of d1-4-(benzyloxy)mandelic acid. M.P. 153°–155° C.

Analysis calc. for $C_{15}H_{14}O_4$ Theory: C, 69.76; H, 5.46; Found: C, 69.96; H, 5.33.

EXAMPLE 2

Resolution of d1-4-(benzyloxy)mandelic Acid to Provide R(–)-(4-benzyloxy)mandelic Acid

To a stirred solution of 185.6 g of d1-4-benzyloxy) mandelic acid in 2500 ml of ethyl acetate at 80° C. was added in one portion 43.6 g of R(+)-α-methyl-benzylamine. The reaction mixture was cooled to room temperature, and the precipitated solid which had formed was collected by filtration and washed with fresh ethyl acetate. The solid was recrystallized twice from a solution of ninety percent ethanol in water to provide 91.4 g of the R(+)-α-methylbenzylamine salt of R(–)-4-(benzyloxy)mandelic acid. M.P. 208.5°–209.5° C. $[\alpha]_D$ –38.6°, $[\alpha]_{365}$ –155.3° (MeOH)

Analysis calc. for $C_{23}H_{25}NO_4$ Theory: C, 72.80; H, 6.64; N, 3.69; Found : C, 72.95; H, 6.83; N, 3.95.

To a stirred suspension of 91.4 g of the above-named salt in 2000 ml of ethyl acetate was added 150 ml of ten percent aqueous hydrochloric acid solution. The aqueous acid solution was separated, and the organic layer washed with water and dried. Removal of the solvent by evaporation under reduced pressure afforded 54.5 g of R(–)-4-(benzyloxy) mandelic acid, ie. R(–) -2-(4-benzyloxyphenyl)-2-hydroxyacetic acid. M.P. 155°–161° C. $[\alpha]_D$ –102.2°; $[\alpha]_{365}$ –410.6° (MeOH)

Analysis calc. for $C_{15}H_{14}O_4$ Theory: C, 69.76; H, 5.46; Found: C, 69.67; H, 5.41.

EXAMPLE 3

Preparation of d1-1-methyl-3-(4-benzyloxyphenyl) propylamine

A solution of 40.0 g of methyl 2-(4-benzyloxyphenyl) ethyl ketone and 160 ml of anhydrous ammonia in 300 ml of ethanol was heated at 75° C. and stirred for two hours. After cooling the reaction mixture to room temperature, 4.0 g of Raney nickel was added in one portion, and the reaction mixture then was stirred at 25° C. for twelve hours under a hydrogen atmosphere at 300 psi. The reaction mixture next was filtered and the filtrate was concentrated by evaporation of the solvent under reduced pressure to provide an oil. The oil was dissolved in 120 ml of 3N hydrochloric acid, from which the product as a hydrochloride salt precipitated. The salt so formed was collected by filtration and recrystallized from methanol and toluene to provide 36.2 g of d1-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride. M.P. 195–197.5° C.

EXAMPLE 4

Resolution of d1-1-methyl-3-(4-benzyloxyphenyl) propylamine to provide R-(–)-1-methyl-3-(4-benzyloxyphenyl)propylamine

A solution of 629.3 g of d1-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride was converted to the free amine by reaction with 95 g of sodium hydroxide in 400 ml of water. The free amine was then dissolved in 2000 ml of methylene chloride and added to a solution of 328 g of D-(–)-mandelic acid in 1000 ml of methanol. The mandelic acid salt of the free amine precipitated out of solution and was recrystallized three times from methanol to provide 322 g of the R-mandelic acid salt of R-1-methyl-3-(4-benzyloxyphenyl)propylamine. M.P 166°–167° C. $[\alpha]_D$ –30°, $[\alpha]_{365}$ –119° (MeOH).

The salt so formed was converted to R-1-methyl-3-(4-benzyloxyphenyl)propylamine as the free base by reaction with aqueous sodium hydroxide.

EXAMPLE 5

R,R-N-[2-(4-Benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl) propylamine

A solution of 93.9 g of R-1-methyl-3-(4-benzyloxyphenyl)propylamine in 500 ml of N,N-dimethylformamide containing 63.0 g of 1-hydroxybenzotriazole and 104.6 g of R-2-(4-benzyloxyphenyl)-2-hydroxyacetic acid was cooled to 0° C. and stirred while a solution of 83.6 g of N,N'-dicyclohexylcarbodiimide in 300 ml of dimethylformamide was added dropwise over one hour. The reaction mixture was stirred for twelve hours at 3° C. and then was diluted with 10 ml of water, stirred for an additional hour, and then cooled to –30° C. in an ice-acetone bath. The reaction mixture was filtered to remove dicyclohexylurea, and then the filtrate was concentrated by evaporation of the solvent under reduced pressure. The concentrated solution was diluted with ethyl acetate and washed with saturated aqueous sodium carbonate solution, with water, with 300 ml of 1N hydrochloric acid, and again with water. The organic layer was dried and the solvent was removed by evaporation under reduced pressure to provide the product as a white solid. The solid was recrystallized once from acetonitrile and again from methanol to provide 159.7 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine. M.P. 145°–148° C. $[\alpha]_D$ –15.9°, $[\alpha]_{365}$ –50.1° (MeOH).

Analysis calc for $C_{32}H_{33}NO_4$ Theory: C, 77.55; H, 6.71; N, 2.83; Found: C, 77.04; H, 6.84; N, 2.53.

EXAMPLE 6

R,R-N-[2-(4-Benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine

To a stirred solution of 10.0 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-

benzyloxyphenyl)propylamine in 500 ml of freshly distilled tetrahydrofuran under a nitrogen gas atmosphere was added dropwise over thirty minutes 41 ml of 2 molar borane-dimethyl sulfide complex in tetrahydrofuran. The reaction mixture was stirred at 25° C. for twenty hours, and then was heated to reflux and stirred for an additional three hours. After cooling the reaction mixture to 25° C. and stirring for another eighteen hours, the excess borane was decomposed by the slow portion-wise addition of 400 ml of methanol. The solvent was then removed from the reaction mixture by evaporation under reduced pressure to provide the product as an oil. The oil so formed was dissolved in 250 ml of hot methanol, and after concentrating the volume to 125 ml, the product began crystallizing out of solution. The crystalline product was collected by filtration and recrystallized twice from methanol to provide 6.65 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine. M.P. 119°–123.5° C.

The amine so formed was dissolved in methanol and added to a solution of ethereal hydrogen chloride, thereby providing 6.49 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl) propylaminium chloride. M.P. 214.5°–216° C. $[\alpha]_D$ –13.4°, $[\alpha]_{365}$ –30.2° (MeOH).

Analysis calc. for $C_{32}H_{36}NO_3Cl$ Theory: C, 74.19; H, 7.00; N, 2.70; Cl, 6.84; Found: C, 74.20; H, 6.98; N, 2.65; Cl, 6.63.

EXAMPLE 7

R,R-1-(4-Hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride, also named as R,R-N-[2-(4-Hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl) propylaminium chloride

A mixture of 51.6 g of R,R-N-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl) propylaminium chloride and 5.0 g of Raney nickel in 2 liters of ethanol and 2 liters of ethyl acetate was stirred at 25° C. for four and one-half hours under a hydrogen atmosphere of 60 psi. The reaction mixture was then filtered to remove the residual Raney nickel, and the filtrate was concentrated to an oil by evaporation of the solvent under reduced pressure, and the oil was crystallized from fresh ethanol and diethyl ether to provide 29.8 g of R,R-N-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl) propylaminium chloride. M.P. 176°–176.5° C. (dec.) $[\alpha]_D$ –22.7°, $[\alpha]_{365}$ –71.2° (3.7 mg/ml MeOH).

Analysis calc. for $C_{18}H_{24}NO_3Cl$ Theory: C, 63.99; H, 7.16; N, 4.15; Found: C, 63.70; H, 7.26; N, 4.32.

EXAMPLE 8

As pointed out above, a preferred embodiment of this invention employs a mixture of all four optical isomers of the compound of Example 7. This racemic mixture can be prepared by the method described above by reaction of dl-4-(benzoyloxy)mandelic acid with dl-1-methyl-3-(4-benzyloxyphenyl)propylamine in the presence of DCC to give racemic 1-(4-benzyloxyphenyl)-2-oxo-2-[1-methyl-3-(4-benzyloxyphenyl)propylamino]ethanol. Reduction of the latter compound and subsequent removal of the benzyl groups provides racemic 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol. This compound is more preferably prepared by the following procedure.

A solution of 32.8 g. (0.2 m) of methyl 2-(4-hydroxyphenyl)ethyl ketone and 42.6 g. (0.2 m) of 1-(4-hydroxyphenyl)-2-aminoethanol in 380 ml. of ethanol containing 3.8 g. of five percent palladium on carbon was stirred for sixteen hours at 60° C. under hydrogen at 55 psi. The reaction mixture was then filtered, and the filtrate was diluted by addition of 350 ml. of water. The aqueous mixture was concentrated to a volume of about 400 ml., and then washed with dichloromethane. The aqueous mixture was acidified by addition of 50 ml. of conc. hydrochloric acid. After standing at room temperature for two hours, the aqueous acid mixture was filtered and the filter cake was washed with 40 ml. of ice water and dried at 50° C. in vacuum to provide 47 g. of 1-(4-hydroxyphenyl-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride. M.P. 124°–129° C.

Analysis calc. for $C_{18}H_{24}NO_3Cl$ Theory: C, 63.99; H, 7.16; N, 4.15; Cl, 10.49. Found: C, 63.77; H, 6.80; N, 3.91; Cl, 10.68.

^{13}C NMR studies demonstrated the product to be comprised of 51% RR,SS diastereamer and 49% RS,SR diastereomer.

EXAMPLE 9

1-Phenyl-2-[1-methyl-3-(4-nitrophenyl) propylamino]ethanol

A solution of 5.0 g. (25.9 mM) of 2-amino-1-phenylethanol and 3.55 g. (25.9 mM) of methyl 2-(4-nitrophenyl)ethyl ketone in 60 ml. of toluene containing 10 mg. of para-toluenesulfonic acid was heated at reflux for six hours in a flask equipped with a Dean-Stark trap. The water that formed during the reaction was removed via the trap, and then the reaction mixture was cooled to room temperature and concentrated to dryness by evaporation of the solvent under reduced pressure. The solid product that remained was dissolved in 50 ml. of tetrahydrofuran and the solution was heated to reflux. A solution of 13.5 ml. of 2N borane-methyl sulfide complex in tetrahydrofuran was then added dropwise to the reaction mixture, and the mixture was refluxed for an additional ninety minutes. After cooling the reaction mixture to room temperature, it was diluted by addition of diethyl ether saturated with hydrogen chloride. The precipitate that formed was collected by filtration and crystallized from ethanol and diethyl ether to give 3.29 g. of 1-phenyl-2-[1-methyl-3-(4-nitrophenyl)-propylamino] ethanol hydrochloride. M.P. 203°–213° C.

Analysis calc. for $C_{18}H_{23}ClN_2O_3$ Theory: C, 61.62; H, 6.61; N, 7.98; Cl, 10.11. Found: C, 61.76; H, 6.62; N, 7.76; Cl, 10.13.

EXAMPLE 10

1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]ethanol

A solution of 32.6 g. (0.2 m) of 1,1-dimethyl-3-phenylpropylamine and 22.9 g. (0.1 m) of 2-(4-methoxyphenyl)-2-oxoethyl bromide in 75 ml. of tetrahydrofuran was heated at reflux for thirty-six hours. The reaction mixture was then cooled and added to 2 liters of diethyl ether. The precipitate was removed by filtration, and the filtrate was acidified with hydrobromic acid to give 18.15 g. of 1-(4-methoxyphenyl)-1-oxo-2-(1,1-dimethyl-3-phenylpropylamino)ethane hydrobromide. M.P. 174°–178° C.

The compound thus formed was dissolved in 85 ml. of glacial acetic acid containing 35 ml. of hydrobromic acid, and the solution was heated at reflux for nine hours. The

solution was then cooled and the solvent was removed by evaporation to provide, following crystallization from ethanol and diethyl ether, 7.8 g. of 1-(4-hydroxyphenyl)-1-oxo-2-(1,1-dimethyl-3-phenylpropylamino)ethane hydrobromide. M.P. 228°–230° C.

Catalytic hydrogenation of 5.0 g. of the compound from above in 44 ml. of ethanol containing 1.25 g. of five percent palladium on carbon afforded, following crystallization from acetone and diethyl ether, 2.3 g. of 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-phenylpropylamino)ethanol hydrobromide. M.P. 168°–170° C.

Analysis calc. for $C_{19}H_{26}BrNO_2$ Theory: C, 60.00; H, 6.89; N, 3.68. Found: C, 60.28; H, 6.67; N, 3.62.

EXAMPLE 11

1-(3-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-fluorophenyl)propylamino]ethanol

To a stirred solution of 67.2 g. (0.22M) of 2-(3-benzyloxyphenyl)-2-oxoethyl bromide in 200 ml. of acetonitrile was added a solution of 54.3 g. (0.20M) of N-benzyl-1,1-dimethyl-3-(4-fluorophenyl)propylamine in 600 ml. of acetonitrile containing 42 ml. (0.22M) of diisopropylethylamine. The reaction mixture was stirred for about six hours at reflux, and then was cooled and stored at room temperature for forty-eight hours. The reaction mixture was next diluted by addition of aqueous sodium hydroxide, and the organic solvents were removed by evaporation under reduced pressure. The aqueous alkaline mixture was extracted with ethyl acetate, which was then washed with water, dried, and concentrated to dryness to give an oil. The oil was dissolved in ethanol and diethyl ether and converted to the hydrochloride salt by addition of excess hydrogen chloride. The precipitated solid was collected by filtration and recrystallized from ethyl acetate to give 51.3 g. of 1-(3-benzyloxyphenyl)-1-oxo-2-[(N-benzyl)-1,1-dimethyl-3-(4-fluorophenyl)-propylamino]ethane hydrochloride. M.P. 137°–145° C.

The compound thus prepared was reduced by reaction with 16 g. of sodium borohydride in ethanol. Isolation of the product, followed by conversion to the hydrochloride salt and crystallization from diethyl ether afforded 55.0 g. of 1-(3-benzyloxyphenyl)-2-[(N-benzyl)-1,1-dimethyl-3-(4-fluorophenyl) propylamino]ethanol hydrochloride. M.P. 186.5°–191° C.

A solution of 10.0 g. of the product thus produced in 200 ml. of ethanol containing 3.0 g. of Raney Nickel was shaken for two hours at 25° C. under hydrogen at 44 psi. The reaction mixture was then filtered, and the solvent was removed from the filtrate by evaporation under reduced pressure to give a white solid. The solid was triturated with ethyl acetate and air dried to provide 5.9 g. of 1-(3-hydroxyphenyl)-2-[1,1-dimethyl-3-(4-fluorophenyl) propylamino]ethanol hydrochloride. M.P. 196.5°–198.5° C.

Analysis calc. for $C_{19}H_{25}ClFNO_2$ Theory: C, 64.49; H, 7.12; N, 3.96; Cl, 10.02. Found: C, 64.29; H, 6.97; N, 4.06; Cl, 9.89.

EXAMPLE 12

1-(4-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol

A suspension of 10.0 g. (50 mM) of 1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamine and 15.0 g. (50 mM) of 1-(4-benzyloxyphenyl)-1-oxoethyl bromide in 1000 ml. of acetonitrile containing 32.0 g. (0.3M) of sodium carbonate and 100 ml. of water was stirred for one hour at 25° C. The precipitate that formed was collected by filtration, washed with water and with diethyl ether, and air dried to provide 8.0 g. of 1-(4-benzyloxyphenyl)-1-oxo-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethane. M.P. 184°–187° C. This product was converted to the hydrochloride salt by reaction with hydrogen chloride in diethyl ether. M.P. 219°–224° C.

The compound thus prepared was reacted with sodium borohydride in methanol to provide, following conversion to the hydrochloride salt and crystallization from methanol and diethyl ether, 5.8 g. of 1-(4-benzyloxyphenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride. M.P. 141°–143° C.

Reaction of the above compound with hydrogen in the presence of Raney Nickel effected cleavage of the hydroxy protecting group to afford, following crystallization of the hydrochloride salt, 1.3 g. of 1-(4-aminocarbonylphenyl) propylamino]ethanol hydrochloride. M.P. 185° C. (dec.)

Analysis calc. for $C_{20}H_{27}ClN_2O_3$ Theory: C, 63.40; H, 7.18; N, 7.39; Cl, 9.36. Found: C, 63.26; H,.7.01; N, 7.45; Cl, 9.42.

The compounds of Examples 13 and 14 were prepared by the general procedure of Example 12.

EXAMPLE 13

1-(27Fluorophenyl)-2-[1,1-dimethyl-3-(4-aminocarbonylphenyl)propylamino]ethanol hydrochloride

M.P. 227°–230° C.

EXAMPLE 14

1-(3-Hydroxyphenyl)-2-[1,1-dimethyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrobromide

M.P. 161°–165 ° C.

EXAMPLE 15

1-Phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl) propylamino]ethanol hydrochloride

Methyl 2-(4-methylthiophenyl)ethyl ketone was oxidized by reaction with m-chloroperbenzoic acid to give methyl 2-(4-methylsulfonylphenyl)ethyl ketone. A solution of 6.73 g. of 2-amino-1-phenylethanol and 11.10 g. of methyl 2-(4-methylsulfonylphenyl)ethyl ketone in 500 ml. of toluene containing 200 mg. of p-toluenesulfonic acid was heated at reflux for twenty-four hours. The reaction mixture was cooled and the solvent was removed by evaporation to give the Schiff base 1-phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl)propylimino]ethanol. The Schiff base thus prepared was reacted with 3.7 g. of sodium borohydride in 500 ml. of ethanol at 0° C. for sixteen hours. The reaction mixture was diluted by addition of 50 ml. of acetone and 20 ml. of 3N hydrochloric acid. The mixture was concentrated to an oil by evaporation of the solvent. The oil crystallized upon standing at room temperature. Recrystallization of the product from 200 ml. of hot ethanol afforded 8.96 g. (48% yield) of 1-phenyl-2-[1-methyl-3-(4-methylsulfonylphenyl) propylamino]ethanol hydrochloride. M.P. 164°–170° C.

Analysis calc. for $C_{19}H_{26}ClNO_3S$ Theory: C, 59.44; H, 6.83; N, 3.65; Cl, 9.23; S, 8.35. Found: C, 59.28; H, 6.57; N, 3.70; Cl, 9.36; S, 8.11.

EXAMPLE 16

Premix for Chickens

Ingredient	% by weight
1-(4-hydroxyphenyl)-2-[1,1-dimethyl-3-phenylpropylamino]-ethanol succinate	25
Ground Corn	74
Sodium Chloride	1
	100

EXAMPLE 17

Premix for ruminants

Ingredient	% by weight
1-(2-fluorophenyl)-2-[1,1-dimethyl-3-(4-aminocarbonyl-phenyl)propylamino]ethanol	30
Ground yellow corn	60
Alfalfa meal	10
	100

EXAMPLE 18

Premix for Swine

Ingredient	% by weight
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol hydrochloride	10
Soybean mill run	88
Mineral oil	2
	100

The above ingredients are blended to uniformity to provide a dry flowable premix that can be admixed with a typical animal feed ration at a rate to provide about 20 ppm of active ingredient in the final feed ration. For example, the premix can be added to the following swine grower ration for convenient oral administration of the β-phenethanolamine to swine.

Ingredient	% by weight	lbs/Ton
Corn, yellow, ground	76.70	1534
Soybean Oil Meal, solvent extracted, dehulled	19.35	387
Calcium Carbonate	1.20	24
Dicalcium Phosphate, feed grade	1.20	24
Salt (sodium chloride)	0.50	10
Trace mineral premix, AN-03[1]	0.10	2
Swine Vitamin Premix, SW-03[2]	0.65	13
Vitamin A Premix, 3M USP units/lb.[3]	0.05	1
Methionine Hydroxy Analogue, 93%	0.20	4
Selenium Premix[4]	0.005	1
	100.00	2000

-continued

Ingredient	% by weight	lbs/Ton

[1]Each Kg of premix contains: 50 g. manganese as manganese sulfate; 100 g. zinc as zinc carbonate; 50 g. iron as ferrous sulfate; 5 g. copper as copper oxide; 1.5 g. iodine as potassium iodide and 150 g. maximum and 130 g. minimum calcium as calcium carbonate.
[2]Each Kg of premix contains: 77,161 IU Vitamin D_2; 2,205 IU Vitamin E; 411 mg. riboflavin; 1,620 mg. pantothenic acid; 2,205 mg. niacin; 4.4 mg. Vitamin B_{12}; 441 mg. Vitamin K; 19,180 mg. choline; 110 mg. folic acid; 165 mg. pyridoxine; 110 mg. thiamine; 22 mg. biotin.
[3]Each Kg of premix contains 6,613,800 IU Vitamin A.
[4]Each Kg of premix contains 200 mg. of selenium as sodium selenite.

EXAMPLE 19

Feed Ration for Lambs

Ingredient	Percent	lbs/T
Yellow corn	61.00	1220.0
Corn cobs	20.00	400.0
Alfalfa Meal, dehydrated	5.40	108.0
Soybean oil meal	8.00	160.0
Urea, feed grade	0.50	10.0
Molasses, cane	3.00	60.0
Dicalcium phosphate	0.43	8.6
Salt	0.30	6.0
Calcium carbonate	0.14	2.3
Trace mineral premix[1]	0.03	0.6
Vitamin A + D_3 Premix[2]	0.10	2.0
Vitamin E Premix[3]	0.10	2.0
1-(4-Hydroxyphenyl)-2-(1,1-dimethyl-3-phenylpropylamino)-ethanol	1.00	20.0
	100.00	2000.0

[1]Trace mineral premix contains: 2.5% manganese as manganese oxide, 0.07% iodine as potassium iodide, 0.3% cobalt as cobalt carbonate, 0.5% copper as copper oxide, and 20.0% zinc as zinc sulfate.
[2]Each pound of vitamin A and D_3 premix contains 2,000,000 USP units Vitamin A and 225,750 USP units Vitamin D_3.
[3]Each pound of Vitamin E premix contains 20,000 IU Vitamin E.

The compounds to be employed in the method of this invention have demonstrated efficacy in animal tests designed to establish beneficial nutritional effects. In one test designed to show lipolytic activity, normal swine, either barrows or gilts, were employed to analyze the effect of compounds on blood glucose, insulin, and non-esterified fatty acids (NEFA).

Test animals were maintained in metabolism crates, and following a period of adaptation, catheters were placed in their femoral veins. Prior to administration of the test compounds, all animals were fasted for a period of forty hours. Such fasting causes an elevation of NEFA's in the blood. On the day of the test, all animals were fed a normal feed ration, and one group of animals were held as controls while another group of animals received a test compound. The test compounds were administered at 200 mcg/kg intravenously, or orally at 1 mg/kg. Blood samples were taken from each animal immediately prior to treatment and then at one hour intervals for a period of six hours following treatment. The blood plasma was analyzed for glucose, insulin and NEFA content.

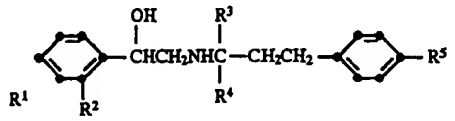
When the fasted pigs were fed the normal feed ration without a test compound, the NEFA levels in the blood drop dramatically and remained low. A β-phenethanolamine as defined herein caused either an elevation in NEFA's, or inhibited the drop in NEFA's. Blood levels of glucose and insulin were also elevated with the β-phenethanolamines.

The following Table presents the lipolytic activity of several preferred β-phenethanolamines when evaluated

according to the test described above. The results are averages of several tests.

TABLE I

Lipolytic Activity (increase in NEFA's)



R^1	R^2	R^3	R^4	R^5	% increase in NEFA's over control	% increase in glucose over control
H	H	H	CH_3	SO_2CH_3	131	9
p-OH	H	CH_3	CH_3	H	445	48
m-OH	H	CH_3	CH_3	H	71	31
m-OH	H	CH_3	CH_3	F	28	72
p-OH	H	CH_3	CH_3	OH	141	35
p-OH	H	CH_3	CH_3	$CONH_2$	18	169
m-OH	H	CH_3	CH_3	OH	68	40
H	H	H	H	NO_2	199	7
p-OCH_3	H	CH_3	CH_3	H	84	25
p-OCH_3	H	CH_3	CH_3	OH	249	5
H	H	H	CH_3	NO_2	1458	27

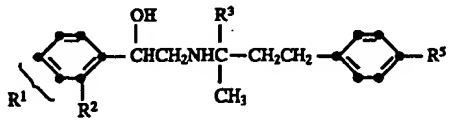
A ten day in vivo study was employed to determine the effect of β-phenethanolamines on feed efficiency and rate of growth. In these studies, barrows and gilts weighing approximately 60 kg were maintained in individual pens. Each treatment was replicated six times in randomly assigned animals, with each test animal forming an experimental unit. A group of control animals received a normal swine grower feed ration comprising the following ingredients:

Ingredient	% by weight
Ground yellow corn	76.70
Soybean oil meal	19.35
Calcium carbonate	1.20
Dicalcium phosphate	1.20
Salt	0.50
Trace mineral premix	0.10
Swine Vitamin premix	0.65
Vitamin A premix, 3M USP units/lb.	0.05
Methionine Hydroxy analogue, 93%	0.20
Selenium premix	0.05
	100.00

The test animals received the same feed ration plus the test compound. All animals received feed and water ad libitum. All animals were weighed on day 1 and again on day 10, and feed consumption was measured by recording all feed issued and any remaining feed on day 10. The results of two series of this 10 day test for several β-phenethanolamines are given in Table II. In the Table, the column labelled "ADG" is the average daily weight gain in pounds; "ADF" is the average daily feed consumption (in pounds) by the test animals; and F/G is the feed efficiency calculated as ADF divided by

TABLE II

Growth Promotion and Feed Efficiency



	R^1	R^2	R^3	R^5	dose ppm	ADG	ADF	F/G
Experiment I	Control					1.60	4.7	2.98
	p-OH	H	H	OH	20	2.19	5.0	2.33
	H	H	H	NO_2	20	1.78	4.22	2.37
Experiment II	Control					1.34	4.16	3.22
	p-OH	H	CH_3	H	20	1.60	4.26	2.66
	m-OH	H	CH_3	F	20	1.52	4.57	3.01

The β-phenethanolamines to be employed in the method of this invention can be administered in combination with other compounds known to have a beneficial effect upon animals. Typical compounds to be co-administered with the β-phenethanolamines include antibiotics, for example any of the tetracyclines, tylosin, penicillins, cephalosporins, polyether antibiotics, glycopeptides, orthosomycins and related compounds commonly administered to swine, poultry, ruminants and the like. A preferred combination to be employed in the present method is an antibiotic such as tylosin or a tetracycline, together with 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol. Such combinations will comprise the respective components in a ratio of about 1 to about 2 parts by weight of β-phenethanolamine and about 1 to about 10 parts by weight of the partner component.

In a typical treatment, 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol was evaluated in a 42-day study employing finishing swine. Each treatment was replicated four times, with three pigs per replication. All treatments included a normal feed diet plus tylosin at 40 g/T. The animals were tested for growth performance and feed efficiency enhancement. Carcass quality was determined by analysis for fat and muscling. The results of the study are given in Table III. Both β-phenethanolamine treatments resulted in improved growth performance and carcasses with less fat and more muscle.

TABLE III

Growth Promotion, Feed Efficiency and Carcass Quality

		β-phenethanolamine[2]			
	Control[1]	20 g/T	% change	40 g/T	% change
ADG	1.94	2.07	(6.7)	2.05	(5.7)
ADF	6.28	6.63	(5.6)	6.64	(5.7)
F/G	3.24	3.20	(−1.2)	3.24	(0)

TABLE III-continued

Growth Promotion, Feed Efficiency and Carcass Quality

	β-phenethanolamine[2]				
	Control[1]	20 g/T	% change	40 g/T	% change
Live Wt. at Slaughter, lb	217.0	223.0	(2.8)	221.0	(1.8)
Chilled Carcass Wt., lb	154.6	160.5	(3.8)	159.8	(3.4)
Fat Depth at 10th Rib, in	1.15	1.09	(–5.2)	1.05	(–8.7)
Loin Eye Area Sp., in	4.64	4.91	(5.8)	4.84	(4.3)
Estimated Pounds of Fat Free Muscle[3]	74.2	78.8	(6.1)	78.4	(5.7)

[1]all diets contained 40 g/T of tyrosin
[2]1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]-ethanol hydrochloride
[3]A regression equation was employed in arriving at the numerical predictions of carcass muscle (J. Animal Science, 1977, Vol. 44:8–17).

The data reported in Table III further demonstrates that the β-phenethanolamines described herein promote growth, improve feed efficiency and improve leaness.

In a similar study conducted over a 61 day period, a group of control animals received a normal daily feed ration with no additive. Another group of animals received the feed ration plus tylosin at 40 g/T, while another group received the feed ration plus 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride (compound A) at 20 g/T. A final group of finishing swine received the feed ration plus the combination of 40 g/T of tylosin and 20 g/T of the phenethanolamine. The results of this trial are given in Table IV.

TABLE IV

	Control	Tylosin	A	Tylosin + A
ADG	1.63	1.64	1.36	1.50
ADF	5.64	5.77	5.10	5.38
F/G	3.46	3.51	3.77	3.59
Slaughter Wt, (lbs)	210	211	193	201
Carcass Wt, (lbs)	150.3	151.5	140.1	146.3
Fat-Depth, 10th rib, (in)[1]	0.96	0.96	0.80	0.85
Loin Eye Area (in^2)[1]	4.60	4.68	4.92	5.00
Est. % Muscle[2]	49.2	49.2	51.4	51.2
Est. Pounds Muscle[2]	75.3	76.5	74.1	76.8

[1]These results are based upon measurement of fat at the 10th rib after the carcass is split in half across the backbone.
[2]A regression equation is employed in arriving at the numerical predictions of carcass muscle (J. Animal Science, 1977, Vol. 44:8–17).

As in the previous study, both phenethanolamine treatments resulted in carcasses with less fat and more muscle. It should also be noted that the estimated amount of carcass muscle produced with the Tylosin +A treatment was similar to that produced in the control and the Tylosin treatment alone. This result was achieved, however, with less feed consumption than either the control or the Tylosin treatments.

Additional studies have been carried out to demonstrate the anabolic effect of β-phenethanolamines in swine. The effect of the compounds on nitrogen retention in finishing barrows was determined. Nitrogen retention is the difference between nitrogen intake and nitrogen excreted. Increased nitrogen retention is known to be associated with increased anabolic activity, resulting in improved carcass muscling and leanness.

In a typical study, barrows weighing about 172 pounds (78 Kg) were orally administered various doses of 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl) propylamino]ethanol hydrochloride (Compound A). All animals received water and a constant amount of normal swine feed ration. The results of this study are presented in Table V, and show that all β-phenethanolamine treatments improved nitrogen retention compared to controls.

TABLE V

	Nitrogen Retention	
Treatment	Animals per treatment	Nitrogen Retained (g/day)
Control	6	21.0
Compound A (5 g/T)	3	23.6
Compound A (10 g/T)	3	23.9
Compound A (20 g/T)	3	25.0

As pointed out above, the method of this invention can be practiced with individual isomers of β-phenethanolamines or with mixtures of isomers and diastereomers. In a study to determine the effect on weight gain and feed efficacy of various mixtures of diastereomers, barrows initially weighing about 177 pounds were fed a normal swine diet plus a β-phenethanolamine at 20 g/T of feedstuff. Each treatment was replicated in twelve individually fed animals. The results are presented in Table VI and show that growth performance was improved by both β-phenethanolamine treatments with very little change in feed intake.

TABLE VI

Treatment	Average Daily Feed (lbs)	Average Daily Gain (lbs)
Control	5.89	1.58
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride 57.5% RR, SS 42.5% RS, SR	5.94	2.15
1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)-propylamino]ethanol hydrochloride 47% RR, SS 53% RS, SR	5.86	1.95

The data in Table VI demonstrates that the method of improving feed efficency and promoting growth can be practiced with any desired mixture of β-phenethanolamine optical isomers.

The efficacy of the β-phenethanolamines described herein also has been demonstrated in poultry. In a typical study, broilers that were twenty-one days old were administered an oral dosing of a β-phenethanolamine in their normal daily

feed ration. All animals received the following broiler finisher ration:

Ingredients	% by weight	lbs/T
Ground yellow corn	66.40	1328.00
Animal-vegetable fat	1.53	30.60
Corn Glut. meal (60%)	4.00	80.00
Soybean meal (48%)	19.19	383.80
Fish meal-menhaden	2.50	50.00
Dicalcium phosphate	1.01	34.20
Feather meal-Hydr.	2.50	50.00
Ground limestone	0.83	16.60
Salt	0.30	6.00
Vitamin Premix[1]	0.50	10.00
Trace mineral premix[2]	0.10	2.00
Methionine Hyd. Anal.	0.15	3.00
Lysine HCl	0.29	5.80
	100.00	2000.00

[1]Vitamin prenix provides 3000 IU of vitamin A, 900 ICU of vitamin D_3, 40 mg. of vitamin E, 0.7 mg. of vitamin K, 1000 mg of choline, 70 mg. of niacin, 4 mg of pantothenic acid, 4 mg of riboflavin, 100 mcg of vitamin B_{12}, 100 mcg of biotin and 125 mg of ethoxyquin per kg of complete feed.
[2]Trace mineral premix provides 75 mg of manganese, 50 mg of zinc, 25 mg of iron and 1 mg of iodine per kg of complete feed.

Test animals received with the above ration varying doses of 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl) propylamino]ethanol hydrochloride (compound A). Each treatment was replicated sixteen times, and the test was terminated when the animals reached fifty-six days of age. The animals were analyzed for weight gain and feed efficiency. The results of this test in broilers is presented in Table VII as mean weight gain and mean feed to gain ratios.

TABLE VII

Growth Performance of Broilers

				Feed Efficiency	
	Dose	Weight Gain		Feed/Gain	% change
Treatment	(g/T)	grams	% improvement	Ratio	from control
Control		1473	0	2.336	0
Compound A	10	1585	7.6	2.292	1.9
Compound A	20	1613	9.5	2.298	1.6
Compound A	40	1550	5.2	2.312	1.0
Compound A	80	1669	13.3	2.221	4.9

The results of this study demonstrate that the β-phenethanolamines described herein are effective in promoting growth and improving feed efficiency in poultry.

The compounds of the invention also have demonstrated efficacy in ruminants. Forty-eight crossbred wether lambs were employed in a test designed to show the effects of Compound A (1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino]ethanol hydrochloride) at varying doses. Sixteen animals were held as controls, while sixteen received 40 ppm of Compound A, and another sixteen received 80 ppm of Compound A. All animals received a normal daily feed ration and water ad libitum. Average daily weight gain and average daily feed consumption after twenty-eight days is given below in Table VIII. The data demonstrates that a β-phenethanolamine as defined herein is effective in promoting growth and improving feed efficiency in ruminants.

TABLE VIII

Growth Performance of Lambs

Treatment	Dose (ppm)	ADG (lbs)	ADF (lbs)	F/G
Control	0	0.414	3.68	8.89
Compound A	40	0.418	3.61	8.64
Compound A	80	0.472	3.57	7.56

We claim:

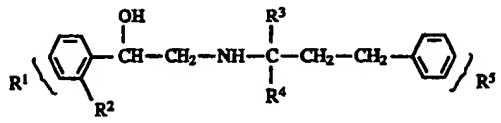
1. A method for promoting the growth of a domesticated warm blooded animal other than a ruminant, swine, or poultry, which comprises administering to the animal an effective amount of 1-(4-hydroxyphenyl)-2-(1-methyl-3-(4-hydroxyphenyl)propylamino)ethanol or an acid addition salt thereof.

2. The method of claim 1 wherein the animal is one raised for human meat consumption.

3. A method for improving the feed efficiency of a domesticated warm blooded animal other than a ruminant, swine, or poultry, which comprises administering to the animal an effective amount of 1-(4-hydroxyphenyl)-2-(1-methyl-3-(4-hydroxyphenyl)propylamino)ethanol or an acid addition salt thereof.

4. The method of claim 3 wherein the animal is one raised for human meat consumption.

5. A method for promoting the growth of a domesticated warm blooded animal which comprises administering to the animal an effective amount of a compound having the formula



wherein

R^1 is hydrogen, hydroxy, or methoxy;

R^2 is hydrogen or fluoro;

R^3 is hydrogen or C_1–C_2 alkyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, fluoro, nitro, hydroxy, SO_2CH_3 or $CONH_2$; provided that R^1 is hydrogen only when R^5 is nitro or SO_2CH_3, or an acid addition salt thereof; excluding the compounds 1-(4-hydroxyphenyl)-2-(1-methyl-3-(4-hydroxyphenyl)propylamino)ethanol and 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-phenylpropylamino)ethanol and their acid addition salts.

6. The method of claim 5 employing 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-(4-hydroxyphenyl)propylamino)ethanol or an acid addition salt thereof.

7. The method of claim 5 wherein the animal is one raised for human meat consumption.

8. The method of claim 7 wherein the animal is a ruminant.

9. The method of claim 7 wherein the animal is a swine.

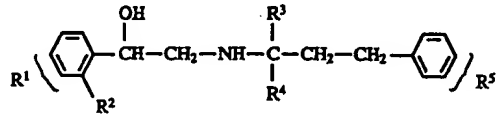
10. The method of claim 7 wherein the animal is poultry.

11. The method of claim 10 employing 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-(4-hydroxyphenyl) propylamino)ethanol or an acid addition salt thereof.

12. The method of claim 11 wherein the poultry is a turkey.

13. The method of claim 11 wherein the poultry is a chicken.

14. A method for improving the efficiency of feed utilization by a domesticated warm blooded animal which comprises administering an effective amount of a compound of the formula



wherein:

R^1 is hydrogen, hydroxy, or methoxy;

R^2 is hydrogen or fluoro;

R^3 is hydrogen or C_1–C_2 alkyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, fluoro, nitro, hydroxy, SO_2CH_3 or $CONH_2$; provided that R^1 is hydrogen only when R^5 is nitro or SO_2CH_3, or an acid addition salt thereof; excluding the compounds 1-(4-hydroxyphenyl)-2-(1-methyl-3-(4-hydroxyphenyl)propylamino)ethanol and 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-phenylpropylamino)ethanol and their acid addition salts.

15. The method of claim 14 employing 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-(4-hydroxyphenyl) propylamino)ethanol or an acid addition salt thereof.

16. The method of claim 14 wherein the animal is one raised for human meat consumption.

17. The method of claim 16 wherein the animal is a ruminant.

18. The method of claim 16 wherein the animal is a swine.

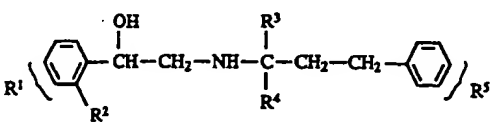
19. The method of claim 16 wherein the animal is poultry.

20. The method of claim 19 employing 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-(4-hydroxyphenyl) propylamino)ethanol or an acid addition salt thereof.

21. The method of claim 20 wherein the poultry is a turkey.

22. The method of claim 20 wherein the poultry is a chicken.

23. A method for improving leanness in a domesticated warm blooded animal which comprises administering to the animal an effective amount of a compound of the formula



wherein:

R^1 is hydrogen, hydroxy, or methoxy;

R^2 is hydrogen or fluoro;

R^3 is hydrogen or C_1–C_2 alkyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, fluoro, nitro, hydroxy, SO_2CH_3 or $CONH_2$; provided that R^1 is hydrogen only when R^5 is nitro or SO_2CH_3, or an acid addition salt thereof; excluding the compounds 1-(4-hydroxyphenyl)-2-(1-methyl-3-(4-hydroxyphenyl)propylamino)ethanol and 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-phenylpropylamino)ethanol and their acid addition salts.

24. The method of claim 23 employing 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-(4-hydroxyphenyl) propylamino)ethanol or an acid addition salt thereof.

25. The method of claim 23 wherein the animal is one raised for human meat consumption.

26. The method of claim 25 wherein the animal is a ruminant.

27. The method of claim 25 wherein the animal is a swine.

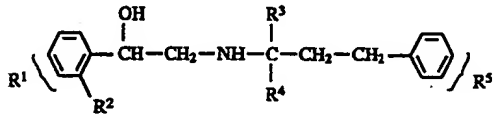
28. The method of claim 25 wherein the animal is poultry.

29. The method of claim 28 employing 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-(4-hydroxyphenyl) propylamino)ethanol or an acid addition salt.

30. The method of claim 23 wherein the animal is a dog.

31. The method of claim 23 wherein the animal is a cat.

32. An animal feedstuff comprising a β-phenethanolamine of the formula



wherein:

R^1 is hydrogen, hydroxy, or methoxy;

R^2 is hydrogen or fluoro;

R^3 is hydrogen or C_1–C_2 alkyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, fluoro, nitro, hydroxy, SO_2CH_3 or $CONH_2$; provided that R^1 is hydrogen only when R^5 is nitro or SO_2CH_3, or an acid addition salt thereof; excluding the compound 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-phenylpropylamino)ethanol and its acid addition salts.

33. The feedstuff of claim 32 wherein the β-phenethanolamine is 1-(4-hydroxyphenyl)-2-(1-methyl-3-(4-hydroxyphenyl)propylamino)ethanol or an acid addition salt thereof.

34. The feedstuff of claim 32 wherein the β-phenethanolamine is 1-(4-hydroxyphenyl)-2-(1,1-dimethyl-3-(4-hydroxyphenyl)propylamino)ethanol or an acid addition salt thereof.

35. The feedstuff of claim 32 containing from about 5 to about 95 percent by weight of the β-phenethanolamine.

36. The feedstuff of claim 35 comprising corncob meal as a carrier.

37. The feedstuff of claim 36 wherein the β-phenethanolamine is 1-(4-hydroxyphenyl)-2-(1-methyl-3-(4-hydroxyphenyl)propylamino)ethanol or an acid addition salt thereof.

38. The feedstuff of claim 37 wherein the β-phenethanolamine is 1-(4-hydroxyphenyl)-2-(1-methyl-3-(4-hydroxyphenyl)propylamino)ethanol hydrochloride.

* * * * *